British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma

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ABSTRACT

These guidelines for the diagnosis and management of cholangiocarcinoma (CCA) were commissioned by the British Society of Gastroenterology liver section. The guideline writing committee included a multidisciplinary team of experts from various specialties involved in the management of CCA, as well as patient/public representatives from AMMF (the Cholangiocarcinoma Charity) and PSC Support. Quality of evidence is presented using the Appraisal of Guidelines for Research and Evaluation (AGREE II) format. The recommendations arising are to be used as guidance rather than as a strict protocol-based reference, as the management of patients with CCA is often complex and always requires individual patient-centred considerations.

EXECUTIVE SUMMARY AND LIST OF RECOMMENDATIONS

The management of CCA should be undertaken at centres with expertise across all relevant specialties, including surgery, interventional radiology, endoscopy, hepatobiliary medicine, oncology and pathology.

Recommendation 1: All patients with CCA discussed at multidisciplinary team (MDT) meetings should be classified as best as possible into either intrahepatic, perihilar or distal CCA. This should be clearly recorded in the MDT outcome discussion.

Strength of recommendation: STRONG
Quality of evidence: MODERATE

Recommendation 2: The requirement to have tissue available for molecular profiling to inform treatment decisions should be considered when immunohistochemistry is planned on lesional biopsy material.

Strength of recommendation: STRONG
Quality of evidence: HIGH

Recommendation 3: A diagnosis of combined hepatocellular-CCA should be made on morphological pathological grounds only.

Strength of recommendation: MODERATE
Quality of evidence: MODERATE

Recommendation 4: All centres managing patients with CCA should have clear established diagnostic pathways for patients presenting with jaundice/biliary obstruction, with streamlined transition to local and regional hepato-pancreatobiliary (HPB) MDT meetings.

Strength of recommendation: STRONG
Quality of evidence: HIGH

Recommendation 5: Having completed imaging, all patients should undergo a detailed review of clinical presentation, examination findings, blood investigations and imaging, ideally at a regionally coordinated hepatobiliary MDT meeting, with prompt assessment of the results and communication with the patient.

Strength of recommendation: STRONG
Quality of evidence: MODERATE

Recommendation 6: Consideration should be given to possible benign causes of biliary tract stricturing/obstruction during MDT discussion, in correlation with appropriate serological investigations and clinical history, to ensure that alternative diagnoses are considered while a pathological diagnosis of CCA is secured.

Strength of recommendation: STRONG
Quality of evidence: MODERATE

Recommendation 7: Contrast enhanced multiphasic CT of the chest, abdomen and pelvis to stage the primary tumour, including assessment of local vascular relationships, should be undertaken for all types of CCA.

Strength of recommendation: STRONG
Quality of evidence: MODERATE

Recommendation 8: Contrast enhanced MRI and magnetic resonance cholangiopancreatography (MRCP) should be undertaken for perihilar and intrahepatic tumours to better delineate the extent of biliary involvement and identify any satellites/intrahepatic metastases.

Strength of recommendation: STRONG
Quality of evidence: MODERATE

Recommendation 9: For tumours involving the more distal extrahepatic duct, MRI is unlikely to add any further information over and above CT.

Strength of recommendation: MODERATE
Quality of evidence: LOW

Recommendation 10: [18F-fluoro-deoxy-glucose positron emission tomography ([18F-FDG-PET]) CT for detection of nodal and distant metastatic disease is recommended as part of staging investigations.

Strength of recommendation: STRONG
Quality of evidence: MODERATE
Recommendation 11: Ultrasound (US) or CT-guided biopsy of the primary intrahepatic tumour or metastatic lesions should be undertaken to acquire a pathological diagnosis following MDT discussion and consensus.  
Strength of recommendation: STRONG  
Quality of evidence: HIGH

Recommendation 12: Before undertaking any endoscopic investigations for a suspected CCA, all patients should have undergone a triple-phase CT scan of the abdomen/pelvis and chest along with dynamic MRI and MRCP if proximal biliary obstruction is suspected.  
Strength of recommendation: STRONG  
Quality of evidence: MODERATE

Recommendation 13: Patients with operable distal malignant tract obstruction (DMTO) should undergo a combination of endoscopic US and endoscopic retrograde cholangiopancreatography (ERCP) to try to confirm a malignant histological diagnosis before proceeding to surgery.  
Strength of recommendation: MODERATE  
Quality of evidence: LOW

Recommendation 14: In a suspected case of operable distal CCA, in the absence of jaundice, a standalone endoscopic ultrasound (EUS) scan should be undertaken first, to avoid the complications of ERCP, which could delay or render the patient inoperable.  
Strength of recommendation: WEAK  
Quality of evidence: LOW

Recommendation 15: In the presence of jaundice and DMTO, where EUS is not available, patients may only be able to have an ERCP and brush cytology in the first instance to confirm the presence of a CCA.  
Strength of recommendation: MODERATE  
Quality of evidence: MODERATE

Recommendation 16: At present biliary biomarkers cannot be recommended as a replacement for cytological and histological standards. However, biliary next-generation sequencing shows great promise and should be taken forward for replicative National Institute for Health Research/UK Research and Innovation (NIHR/UKRI) funded multisite studies.  
Strength of recommendation: MODERATE  
Quality of evidence: MODERATE

Recommendation 17: It should be realised that a cytological/histological confirmation of a malignant biliary tract obstruction (MBTO) is imperfect at present, and in cases where uncertainty remains, a decision on follow-up imaging versus surgery for a definitive diagnosis should be reached only after a full discussion between the patient and the clinician. These guidelines acknowledge that it is acceptable to offer surgery where histological confirmation cannot exclude malignancy with absolute certainty and surgery might provide a cure and a secure diagnosis.  
Strength of recommendation: STRONG  
Quality of evidence: LOW

Recommendation 18: The decision to drain preoperative jaundice in distal CCA causing DMTO should be made in accordance with local hepatopancreatico-biliary (HPB) centre guidance. In cases where rapid access to surgery can be offered, it may be appropriate to bypass biliary drainage at ERCP to avoid ERCP-related complications and postoperative sepsis.  
Strength of recommendation: STRONG  
Quality of evidence: HIGH

Recommendation 19: Patients with DMTO with inoperable disease from distal CCA should undergo an EUS/ERCP or stand-alone ERCP to confirm a pathological diagnosis and have their jaundice palliated.  
Strength of recommendation: STRONG  
Quality of evidence: HIGH

Stronger recommendation: STRENGTH
Recommendation 30: Preoperative preparation, including augmentation of the functional liver remnant (FLR) and biliary drainage, may be required to ensure safe resection.

Strength of recommendation: STRONG
Quality of evidence: HIGH

Recommendation 31: Staging laparoscopy should be used selectively.

Strength of recommendation: STRONG
Quality of evidence: MODERATE

Recommendation 32: R0 resection is the only curative treatment available.

Strength of recommendation: STRONG
Quality of evidence: MODERATE

Recommendation 33: Surgical resection of CCA should be undertaken only at high-volume centres with expertise across all relevant supporting specialties, including interventional radiology, endoscopy, hepatobiliary medicine, oncology and pathology.

Strength of recommendation: STRONG
Quality of evidence: MODERATE

Recommendation 34: Liver transplantation for selected patients with perihilar CCA (pCCA) in the presence of chronic liver disease (most commonly primary sclerosing cholangitis), less than 3 cm in size with no evidence of extrahepatic disease, results in long-term disease-free survival. This is an established indication in an increasing number of centres internationally. There is a need for evaluation of novel neoadjuvant chemoradiation strategies and assessment of long-term outcomes with national protocols and multicentre studies. Liver transplantation in the absence of background chronic liver disease remains an investigational treatment.

Strength of recommendation: MODERATE
Quality of evidence: STRONG

Recommendation 35: Neoadjuvant therapy in uncontrolled studies appears to be effective in controlling disease and selecting patients who are most likely to benefit from transplantation.

Strength of recommendation: MODERATE
Quality of evidence: LOW

Recommendation 36: Transplantation for intrahepatic CCA (iCCA) on a background of chronic liver disease precluding resection should be evaluated prospectively within a national protocol. LAG tumour size criteria to be monitored and modified to improve recruitment for evaluation.

Strength of recommendation: STRONG
Quality of evidence: MODERATE

Recommendation 37: Patients who have undergone surgical resection for CCA should be considered for 24 weeks of adjuvant chemotherapy (currently capecitabine).

Strength of recommendation: STRONG
Quality of evidence: MODERATE

Recommendation 38: The routine use of neoadjuvant chemotherapy in patients with resectable CCA is not recommended.

Strength of recommendation: STRONG
Quality of evidence: LOW

Recommendation 39: Cisplatin plus gemcitabine (CisGem) chemotherapy is recommended as the first-line treatment in patients with advanced biliary tract cancer (BTC). Immunotherapy may be added to CisGem chemotherapy, if approved and available, cognisant of the magnitude of benefit and toxicities.

Strength of recommendation: STRONG
Quality of evidence: HIGH

Recommendation 40: Combination chemotherapy is recommended in patients with adequate performance status following failure of first-line chemotherapy, particularly in the absence of a targetable molecular alteration.

Strength of recommendation: MODERATE
Quality of evidence: HIGH

Recommendation 41: CCA should be subjected to molecular profiling at the earliest opportunity, and results and treatment options should be reviewed by clinicians with appropriate expertise.

Strength of recommendation: STRONG
Quality of evidence: HIGH

Recommendation 42: Consider the use of adjuvant chemotherapy for extrahepatic CCA or gallbladder cancer and a microscopically positive surgical margin resection (R1 resection) with a shared decision-making approach, considering the risk of potential harm and potential for benefit.

Strength of recommendation: MODERATE
Quality of evidence: MODERATE

Recommendation 43: Consider the delivery of stereotactic radiotherapy (SBRT) or proton beam therapy (PBT) in patients with locally advanced inoperable CCA who have received systemic therapy. Modern radiotherapy techniques should be employed to maximise radiotherapy dose and minimise toxicity.

Strength of recommendation: MODERATE
Quality of evidence: LOW

Recommendation 44: Refer patients with symptomatic metastatic disease for consideration of palliative radiotherapy.

Strength of recommendation: MODERATE
Quality of evidence: MODERATE

Recommendation 45: All patients with incurable CCA should have access to a palliative care assessment to fully evaluate their holistic care needs. Evidence suggests that early palliative care involvement is associated with higher health-related quality of life and lower rates of depression. Good symptom control should be delivered alongside active oncology management.

Strength of recommendation: MODERATE
Quality of evidence: MODERATE

Recommendation 46: Development and funding of clinical trials is key to fully evaluate the impact of pharmacological management of symptoms in patients with CCA and different models of care.

Strength of recommendation: MODERATE
Quality of evidence: LOW

Recommendation 47: All patients diagnosed with CCA should have access to a hepatobiliary cancer nurse specialist who can provide expertise and support to the patient and their immediate family.

Strength of recommendation: STRONG
Quality of evidence: MODERATE

Recommendation 48: All patients diagnosed with CCA should have access to a dietician.

Strength of recommendation: STRONG
Quality of evidence: MODERATE

Recommendation 49: All patients diagnosed with CCA should have timely access to high-quality information and should be directed to a dedicated CCA patient charity so that they can access support and information.

Strength of recommendation: STRONG
Quality of evidence: LOW
SCOPE AND PURPOSE
These guidelines have been commissioned on behalf of the British Society of Gastroenterology (BSG) liver section with the aim of updating and assisting clinicians in the diagnosis and management of patients with cholangiocarcinoma. The previous version was published in 2012. These guidelines do not cover gallbladder cancer or neoplasia of the ampulla of Vater/duodenum. Members of the writing committee included: gastroenterologists, hepatologists, transplant physicians, radiologists, hepatobiliary surgeons, hepatobiliary endoscopists, oncologists, histopathologists, patient representatives (from AMMF and PSC Support), and colleagues from Cholangiocarcinoma-UK (a specialist interest group within the British Association for the Study of the Liver, BASL). Where appropriate and feasible, specific clinically applicable recommendations are provided. The guidelines were reviewed and endorsed by the BSG Clinical Standards and Services Committee. We recommend this document be used in conjunction with other BSG guidelines and similar themed publications by other international bodies (such as recommendations from the European Network for the Study of Cholangiocarcinoma (ENS-CCA), the European Association for the Study of the Liver, the International Liver Cancer Association and the European Society for Medical Oncology). We also recommend revision of the guidelines in, at most, 5 years.

EVIDENCE BASE
These guidelines have been produced with a systematic review of publications identified using PubMed Medline, and Cochrane database searches. Each section of the guideline was allocated at least one lead author responsible for performing a comprehensive literature search. The literature search was updated and completed in November 2022 before submission for peer review. Where possible, guidance is based on the highest levels of evidence available. Where no high-quality studies or clear evidence exist, guidance is based on the majority consensus advice of expert opinion in the literature and the writing committee. All recommendations achieved complete consensus following extensive review and discussion among the guideline development group. The grade of evidence is presented according to the international GRADE system as follows:

- High-quality evidence: The authors are very confident that the estimate presented lies very close to the true value. One could interpret it as: there is very low probability of further research completely changing the presented conclusions.
- Moderate-quality evidence: The authors are confident that the presented estimate lies close to the true value, but it is also possible that it might be substantially different. Hence further research might alter the conclusions completely.
- Low-quality evidence: The authors are not confident of the effect estimate and the true value might be substantially different—that is, further research is likely to change the presented conclusions completely.
- Very low-quality evidence: The authors do not have any confidence in the estimate and it is likely that the true value is substantially different from it. One could interpret it as: new research will most probably change the presented conclusions completely.

All members of the guideline working group were asked to complete conflicts of interest declarations. These are available as online supplemental file 1.

BACKGROUND
CCA is a frequently lethal liver cancer arising from epithelial cells, cholangiocytes, anywhere along the biliary tree within or external to the liver.6,7 These are exceptionally desmoplastic tumours and are enmeshed in a dense network of inflammatory cells and extracellular matrix, called the tumour immune microenvironment.6 CCA are typically classified into three subtypes according to their anatomical site of origin: intrahepatic (iCCA), perihilar (pCCA) and distal (dCCA) CCA, with pCCA and dCCA collectively referred to as extraperhepatic CCA (eCCA). iCCA by definition arises within the liver parenchyma, proximal to the second order bile ducts and comprises the second most common form of primary liver cancer globally, after hepatocellular carcinoma (HCC).7 pCCA is localised between the second-degree bile ducts and the insertion of the cystic duct into the common bile duct. dCCA is confined to the common bile duct below the cystic duct insertion. Historic studies report that pCCA accounts for around 50–60% of all CCA, and iCCA accounts for less than 20% of CCA.8 These CCA subtypes are heterogeneous and can vary in their respective clinical presentations, risk factors, routes to diagnosis and clinical management, as well as exhibiting distinct epidemiological, clinical, molecular and genetic characteristics.7

Patients diagnosed with CCA have a high mortality because they typically present too late for surgical resection or transplantation, the only potentially curative options. The clinical presentation of CCA typically depends on its location. pCCA and dCCA are likely to present with obstructive jaundice as well as other constitutional symptoms. iCCA, unless extending into the hilum, tends not to present with jaundice but rather with more non-specific symptoms, such as weight loss, anorexia, abdominal discomfort, nausea and malaise. iCCA can be an incidental finding in around 20% of cases4,5—for example, during surveillance for HCC, or following imaging for another reason. A diagnosis of iCCA can also occur after resection/transplant for a tumour originally deemed to have been something else, such as an HCC or a carcinoma of unknown primary. Diagnosis of anatomical subtype can be clinically and radiologically challenging with some large CCAs which extend into the perihilar or extrahepatic bile ducts, making the site of origin unclear. How to record this uncertainty at MDT meetings in a standardised and systematic way to facilitate epidemiological studies has yet to be resolved.

EPIDEMIOLOGY AND RISK FACTORS
Recommendation 1: All patients with CCA discussed at MDT meetings should be classified as best as possible into either intrahepatic, perihilar or distal CCA. This should be clearly recorded in the MDT outcome discussion.

Strength of recommendation: STRONG
Quality of evidence: MODERATE

Consistent findings reported over the past two decades are the rising incidence and mortality rates for iCCA and declining rates for eCCA.10–13 A recent study of the National Cancer Registration Dataset reported that almost 51 000 BTC were diagnosed in England during 2001–2018.16 CCA were the most commonly diagnosed BTC (63%) followed by gallbladder (23%) and ampulla of Vater (14%). 74% of CCA were ICCA, a higher proportion compared with historic studies. Over 95% of CCA...
Guideline

were diagnosed in patients aged 50 years or older, with the median age at diagnosis being 75. Men and women were approximately equally affected. The age-standardised incidence rate for CCA rose from 2.9 per 100 000 population in 2001–2003 to 4.6 in 2016–2018. The rise in CCA incidence was predominantly in iCCA (figure 1) with age-standardised incidence rates increasing from 2.1 to 3.4 between 2001–2003 and 2016–2018, whereas for the same time period the rise in eCCA was from 0.6 to 1.0. There was evidence of geographical variation in CCA incidence between regional Cancer Alliances in England. The age-standardised mortality rates of CCA rose from 2.6 to 4.9 between 2001–2003 and 2016–2018 in parallel with the incidence rates. The trends for eCCA and iCCA age-standardised mortality rates mirrored those of incidence, with most deaths due to iCCA. The most common route to diagnosis was the emergency route (iCCA 50.4%, eCCA 46.1%), highlighting the late presentation of this disease. Overall survival after diagnosis of CCA was less than 10%.

An important limitation in CCA epidemiology studies is the unknown rate of pCCA specifically, as the main WHO International Classification of Diseases (ICD) coding systems have historically lacked a specific code for pCCA, which has probably been mostly miscoded to iCCA in the past.15 The lack of specific coding for pCCA is to be corrected in the latest version of ICD (2021) but this will not help with understanding the historical rates of pCCA distinct from iCCA and distal eCCA.

Aetiology and risk factors

The global variability of CCA prevalence is thought to be the result of a complex interaction between the host-specific genetic background and the geographical distribution of associated risk factors (table 1). The highest rates of CCA globally are in northeast Thailand and surrounding areas, where the main risk factor is believed to be chronic infection with liver flukes.9 With the absence of liver flukes in the Western world, the most common known risk factor for CCA is primary sclerosing cholangitis (PSC).7 16 Of note, some risk factors are shared by both iCCA and eCCA, while others seem more specific for iCCA or eCCA.7 16 17 Most of the known major risk factors are associated with chronic inflammation of the biliary epithelium and bile stasis. However, the majority of CCA cases in the West are sporadic, without any identifiable risk factors present.

Polymorphisms of host genes encoding enzymes involved in xenobiotic detoxification, DNA repair, multidrug resistance, immune response and folate metabolism have also been linked

| Table 1 Risk factors for cholangiocarcinoma together with type of study (adapted from7 9 11) |
|-----------------|-----------------|-----------------|-----------------|
| Risk factor | Type of study | OR for iCCA | OR for eCCA |
| Caroli’s disease | Population-based study | 38 | 97 |
| Primary sclerosing cholangitis | Population-based study | 22 | 41 |
| Cholelithiasis | Meta-analysis | 26.7 | 34.9 |
| Chronic pancreatitis | Population-based study | 10.1 | 18.6 |
| Chronic hepatitis B | Meta-analysis | 15.3 | 3.8 |
| Chronic hepatitis C | Meta-analysis | 3.4 | 5.9 |
| Inflammatory bowel disease | Meta-analysis | 2.7 | 6.6 |
| Alcohol consumption | Meta-analysis | 4.6 | 2.1 |
| Cholecystolithiasis | Meta-analysis | 4.3 | 2 |
| HAFLD | Meta-analysis | 2.7 | 2.4 |
| Liver fluke (O.viverrini, C. sinensis) | Meta-analysis | 3.2 | 1.8 |
| Cholelithiasis | Meta-analysis | 1.8 | 2.9 |
| NAFLD, non-alcoholic fatty liver disease; RR, relative risk. |

Figure 1 Histopathology of intrahepatic cholangiocarcinoma (iCCA). (A) Small duct iCCA shows an anastomosing tubular architecture. (B) In large duct iCCA, columnar cancer cells with intracytoplasmic mucus are arranged in a ductal structure against the background of fibrotic stroma.

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Intrahepatic bile ducts
⇒ Benign: bile duct adenoma, biliary adenofibroma, serous cystadenoma (microcystic adenoma).
⇒ Premalignant: mucinous cystic neoplasm (MCN), biliary intraepithelial neoplasia (BilIN), intraductal papillomatosis of the bile duct (IPNB).
⇒ Malignant: intrahepatic CCA, IPNB with associated invasive malignancy, MCN with associated invasive malignancy.

Extrahepatic bile ducts
⇒ Benign: none.
⇒ Premalignant: BilIN, MCN, IPNB.
⇒ Malignant: extrahepatic CCA, IPNB with associated invasive malignancy, MCN with associated invasive malignancy, neuroendocrine neoplasms.

Histopathological features of CCA

iCCA can be subdivided into small duct and large duct. Small duct (cholangiocellular) iCCA are typically non-mucin-secreting adenocarcinomas with a ductular or tubular pattern (figure 1A). Cholangiocarcinoma and iCCA with a ductal plate malformation pattern are considered subtypes of small duct iCCA. Large duct iCCA are typically mucin-secreting tubular adenocarcinomas resembling the perihilar and extrahepatic forms (figure 1B). Rare subtypes of eCCA can occur in large duct intrahepatic tumours. Both large and small duct forms of iCCA have a variable fibrous stroma.

Most eCCA are adenocarcinomas of pancreaticobiliary morphology with glandular structures and small groups of cells within a dense desmoplastic stroma. Other types of eCCA include: intestinal-type, foveolar-type, mucinous, signet ring, clear cell, pyloric gland, hepatoid and invasive micropapillary. Rarer types include: squamous cell carcinoma, adenosquamous carcinoma, sarcomatoid carcinoma and undifferentiated carcinoma.

Histological grade
No definitive grading system for CCA has been accepted. The International Collaboration on Cancer Reporting (ICCR) guidance documents a commonly used semiquantitative grading system for iCCA based on the proportion of the tumour that shows gland formation:

- >95% of tumour composed of glands: well-differentiated.
- 50–95% of tumour composed of glands: moderately differentiated.
- <50% of tumour composed of glands: poorly differentiated.

The ICCR guidance also states that the differentiation of pCCA should be classified in the same way as distal large bile duct/pancreatic adenocarcinomas, where grading is determined by the least well-differentiated component rather than the proportion of glandular elements; it should be divided into three grades and is based on gland formation, mucin production, mitotic activity and nuclear features.

Immunohistochemistry
Immunostaining is not essential for the histological diagnosis of CCA and the increasing requirement for molecular profiling of lesional tissue to determine targeted therapies should lead to a reduction in the use of tissue for purely confirmatory immunohistochemical staining. Where imaging is in keeping with CCA, particularly the absence of prior or current extrahepatic malignancy, and the morphology is that of adenocarcinoma, there is no additional diagnostic discrimination offered by immunohistochemical staining.

However, two specific diagnostic scenarios may be aided by targeted immunohistochemistry: (1) When there is a prior history of carcinoma or a possible contemporary extrahepatic primary lesion and the morphology is compatible with both CCA and a metastasis from that prior or putative extrahepatic lesion, immunohistochemistry can be used to confirm the biliary phenotype of cancer cells and differentiate them from metastasis. To aid that particular distinction, CCA is typically positive for cytokeratin (CK) 7 and CK19, and negative for CK20. Large duct iCCA, particularly in cases associated with PSC, sometimes expresses intestinal markers (eg, CK20 and CDX2). C-Reactive protein (CRP) is a highly specific and sensitive marker for iCCA (particularly small duct type), as it is not expressed in adenocarcinomas of other organs. The site of the prior or putative extrahepatic primary lesion allows specific cell lineage–specific transcriptional factor expression to be examined; for example, TTF-1 (expressed in lung and thyroid cancers), PAX8 (renal, thyroid, ovarian and endometrial cancers) and GATA-3 (breast.
and urothelial cancers) are typically negative in CCA. (2) When there is no prior or contemporary extrahaepatic malignancy but the histological features are equivocal in their capacity to distinguish between CCA and HCC, immunohistochemistry may be helpful. Heppar-1, arginase-1 and glypican-3 are often expressed by HCC and not by CCA, although their expression can be lost in poorly differentiated HCCs.

If subclassification of iCCA cannot be made on morphological features alone, a panel of CRP, N-cadherin and S100 calcium binding protein P (S100P) can be useful as CRP/N-cadherin and S100P are commonly expressed in small duct and large duct iCCA, respectively.21–23

**Molecular profile**

Small duct iCCA has distinct molecular features: IDH1/2 mutations (20%), BAP1 mutations (10–20%) and FGFR2 fusions (15%).24–26 In contrast, large duct iCCA and eCCA harbour alterations in KRAS (20%) and SMAD4 (10–20%).24–27 Mutations in TP53 are observed in either type (30%).24–26 FGFR2, NTRK and other fusions or other rearrangements can be diagnosed by RNA sequencing (preferred to immunohistochemistry) or fluorescent in situ hybridisation (FISH), and their identification prior to the use of FGFR inhibitors is essential.28 Mismatch repair protein (MMR) or microsatellite instability (MSI) tests need to be considered if clinically indicated. MMR deficiency is observed in 1–6% of CCA, and those cases often show a solid, mucinous or signet ring cell histological appearance.29–31 NTRK fusions, a category of treatment-related, pan-cancer molecular alterations, are estimated to be detectable in 1% of CCA.32 Table 2 shows the relevant codes from NHS England Genomics that can be used for sequencing. The logistics of molecular testing to guide therapeutic decisions varies within the healthcare systems of the UK’s devolved nations. For example, testing in England is provided by the NHS England Genomic Laboratory Hubs, and the available tests are listed within the test directory (https://www.england.nhs.uk/England Genomic Laboratory Hubs, and the available tests are listed within the test directory (https://www.england.nhs.uk/publication/national-genomic-test-directories).

**Combined hepatocellular–cholangiocarcinoma**

The diagnosis of combined hepatocellular–cholangiocarcinoma requires morphological confirmation of both HCC and adenocarcinoma components.33 Immunohistochemical expressions of hepatocellular markers in otherwise typical iCCA or expressions of CK7/CK19 in HCC are insufficient alone to merit designation of tumours as combined hepatocellular–cholangiocarcinoma. CK7 and CK19 are known to be expressed in 20% and 10% of HCC, respectively.34–35 Most cases of combined hepatocellular–cholangiocarcinoma harbour gene mutations that are identified in HCC (eg, TERT) even within the CCA components.36–37 Tumour, node and metastasis (TNM) staging is currently based on that of iCCA.

**Premalignant neoplasms**

**Biliary intraepithelial neoplasia (BilIN)**

Most cases of large duct CCA are thought to progress from BilIN (previous term, biliary dysplasia) via a multistep carcinogenesis.38 BilIN is diagnosed incidentally in surgically resected specimens or explanted livers. The diagnosis of BilIN in biopsy specimens should be made with caution, as BilIN is unlikely to cause biliary strictures. In contrast, premalignant lesions of small duct iCCA are unknown.

**Intraductal papillary neoplasm of the bile duct (IPNB)**

IPNB is characterised by an intraductal high-papillary proliferation, and is currently classified into two types.39 Type 1 IPNBs develop in intrahepatic (70%) or perihilar ducts (30%), and they are typically associated with cystic or fusiform duct dilatation and mucus overproduction.39–41 Type 2 IPNBs arise in distal (70%) or perihilar ducts (30%), and present with an intraductal solid mass and extensive dilatation of the upstream ducts. The presence of invasive malignancy is confirmed in 50% of type 1 IPNBs and >90% of type 2 IPNBs at the initial presentation.19–41 The gallbladder counterpart of IPNB is referred to as intracholecystic papillary neoplasm.42

**Mucinous cystic neoplasm (MCN)**

This condition was traditionally called biliary cystadenoma. MCN is defined as a cystiform epithelial neoplasm with ovarian-type subepithelial stroma and a lack of communication to the bile duct.42–44 Approximately 50% of MCNs develop in segment IV of the liver.44 Progression to CCA is confirmed in only 5% of surgically resected cases.43

**Pathological diagnosis**

Definitive histology and/or cytology are required to confirm a diagnosis of CCA. Even with successful lesional sampling, distinction of iCCA from metastatic lesions, particularly upper GI, pancreas, or extrahaepatic biliary lesions, is difficult, as discussed earlier. Identification of an invasive component associated with a mucinous cystic neoplasm or intraductal papillary neoplasm on a needle biopsy can also be problematic due to its focal nature.44

Brush cytology from percutaneous or endoscopic procedures has a diagnostic sensitivity of only 30–60%,45–46 meaning negative cytology does not exclude malignancy. Combining cytology

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**Table 2 Available assays through genomics England for cholangiocarcinoma tissue**

<table>
<thead>
<tr>
<th>Code</th>
<th>Assay</th>
<th>Alternate assay</th>
<th>Panel</th>
<th>Patient’s clinical status means they are eligible for an NTRK inhibitor in the event an NTRK rearrangement is detected. Patient’s clinical status means they are eligible for protein kinase inhibitor therapy in the event an FGFR2 fusion is detected.</th>
</tr>
</thead>
<tbody>
<tr>
<td>M220.1</td>
<td>Multitarget NGS panel – structural variant</td>
<td>NTRK1 NTRK2 NTRK3 FGFR2</td>
<td>Structural variant detection Panel</td>
<td></td>
</tr>
<tr>
<td>M220.03</td>
<td>DPYD hotspot</td>
<td>DPYD</td>
<td>Small variant detection Simple targeted mutation testing</td>
<td>Patient planned to receive fluoropyrimidine treatment.</td>
</tr>
<tr>
<td>M220.5</td>
<td>MSI testing</td>
<td>N/A</td>
<td>Microsatellite instability (MSI analysis)</td>
<td>Known CCA when MMR IHC not possible/not performed, according to NICE guidelines for molecular testing to inform therapy choice. Delivery via Pathology in some regions.</td>
</tr>
<tr>
<td>M220.06</td>
<td>Multitarget NGC panel – small variant (IDH1)</td>
<td>IDH1</td>
<td>Small variant detection</td>
<td>Molecular assessment will aid diagnosis or management.</td>
</tr>
</tbody>
</table>

IHC, immunohistochemistry; NGS, next-generation sequencing.
Box 2 Reporting surgical specimens

Surgical resections specimens should be reported systematically—for example, following The Royal College of Pathologists or ICCR reporting guidance.20

The final report should include:
- Tumour site and number: pCCA is defined as arising above the junction of the common hepatic duct and the cysict duct up to the second-order divisions of the right and left hepatic ducts. In iCCA, the number of tumours is a prognostic factor.
- Maximum tumour dimension: increasing tumour size is associated with poorer prognosis.
- Histological tumour type.
- Histological tumour grade.
- Extent of local invasion: required for TNM classification.
- Presence of vascular invasion: an important prognostic factor in iCCA and pCCA, and a component of the TNM classification.
- Presence of precursor lesions.
- Presence of coexistent parenchymal liver disease.
- Margin and lymph node status.
- Pathological staging – American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) TNM 8th edition.20 iCCA, pCCA and dCCA are staged using separate, specific classifications (see online supplemental figures 1–3).

Additional non-core elements should also be reported:
- Tumour growth pattern: mass-forming, periductal infiltrating, intraductal or mixed.
- Presence of perineural invasion: of greatest significance in perihepatic tumours.
- Response to neoadjuvant therapy.

with biopsy increases the diagnostic yield.47 48 The further addition of FISH for polysomy and 9p21 detection increases sensitivity for the detection of malignancy further.38 49 However, in a meta-analysis examining patients with PSC, FISH did not increase the sensitivity to detect malignancy compared with cytology.39 In contrast, the addition of a 28-gene next-generation sequencing panel to pathological assessment of brushings or biopsies increased the sensitivity for the detection of malignancy in patients with and without PSC to over 80%.51

Reporting surgical specimens

Surgical resection specimens should be reported systematically—for example, following The Royal College of Pathologists or ICCR reporting guidance.20 Box 2 provides a summary of how the report should be structured.

PRESENTATION

Recommendation 4: All centres managing patients with CCA should have clear established diagnostic pathways for patients presenting with jaundice/biliary obstruction, with streamlined transition to local and regional HPB MDT meetings.

Strength of recommendation: STRONG
Quality of evidence: HIGH

Recommendation 5: Having completed imaging, all patients should undergo a detailed review of clinical presentation, examination findings, blood investigations and imaging, ideally at a regionally coordinated hepatobiliary MDT meeting, with prompt assessment of and communication to the patient.

Strength of recommendation: STRONG

Quality of evidence: HIGH

Recommendation 6: Consideration should be given to possible benign causes of biliary tract structuring/obstruction during MDT discussion, in correlation with appropriate serological investigations and clinical history, to ensure alternative diagnoses are considered while a pathological diagnosis of CCA is secured.

Strength of recommendation: STRONG
Quality of evidence: MODERATE

Most patients with a CCA will typically present through either emergency services or via referral to a secondary care centre on a 2 week-wait upper GI or jaundice related pathway.14 For patients presenting with eCCA, malignant biliary tract obstruction is a common mode of presentation. Following this, an imaging investigation followed by discussion at a local/regional hepatopancreato-biliary MDT meeting is likely to occur, where a plan will be made on how to achieve: (1) a histological diagnosis, (2) restore bile flow for those patients with jaundice, (3) determine if the patient is an operative candidate, (4) determine what other imaging tests are required for subsequent patient management.

With regards to tissue sampling, a biopsy/cytological sample may be taken from the following sites to secure a diagnosis of CCA: a biliary stricture, periductal/ intrahepatic mass lesion, lymph node metastasis, organ metastasis, pathological serosal fluid sample (pleural fluid, ascites, pericardial fluid) or peritoneal biopsy.

Malignant biliary tract obstruction can present with a wide range of symptoms that include: abnormal liver function tests, jaundice, abdominal pain, tiredness/lethargy, anorexia plus weight loss, thromboembolic disease, hypercalcaemia, paraneoplastic syndromes, abdominal masses/distant organ infiltration, malignant adenopathy, pleural disease, ascites and fever of unknown origin.14 3 At presentation, both distal and hilar biliary strictures essentially remain indeterminate until there is either a positive cytological or histopathological confirmation of CCA, with ultimately, over 80% of such strictures proving to be malignant.52

It is imperative that all patients presenting with possible MBTO have a detailed history taken in reference to age of presentation, country of origin, travel history, constitutional symptoms and weight loss, history of prior HPB surgery, pancreatitis, or inflammatory bowel disease, family history of inflammatory bowel disease, previous investigations to detect possible causes of indeterminate biliary strictures and history of chronic liver disease including viral hepatitis. Benign causes of a cholangiopathy/biliary structuring should also be considered with appropriate collaborative serological testing for diseases which can mimic CCA (box 3).

A detailed family history should also be undertaken to exclude familial cancer syndromes that are associated with CCA. In a study of 267 patients, over 15% of patients had a pathogenic/likely pathogenic somatic variant in a cancer risk gene including: ATM, CHEK2, BAP1, BRCA1, MLH1, BRCA2, PALB2, TP53, APC, CDH1, MSH6, PMS2 and MUTYH.53

If a familial cancer syndrome is suspected from the patient’s genetic history, we would recommend that the patient is referred to a clinical geneticist. Things that might alert clinicians to this include: (1) three or more primary cancers in a single individual, (2) three or more cases of cancer at the same site, (3) any two of: sarcoma, breast cancer, brain tumour, leukaemia or adrenal cortical tumour, in someone under 45, (4) childhood cancer plus one close relative with cancer, (5) any individual or family with an unusual pattern of cancer—for example, rare tumours or young ages at diagnosis, (6) families with a known cancer
predisposition syndrome for example, Li-Fraumeni, Lynch syndrome and Peutz Jeghers, (7) people who meet diagnostic criteria for familial genetic syndromes.

**IMAGING**

**Recommendation 7:** Contrast enhanced multiphasic CT of the chest, abdomen and pelvis to stage the primary tumour, including assessment of local vascular relationships, should be undertaken for all types of CCA.

*Strength of recommendation: STRONG*
*Quality of evidence: MODERATE*

**Recommendation 8:** Contrast enhanced MRI and MRCP should be undertaken for perihilar and intrahepatic tumours to better delineate the extent of biliary involvement and identify any satellites/intrahepatic metastases.

*Strength of recommendation: STRONG*
*Quality of evidence: MODERATE*

**Recommendation 9:** For tumours involving the more distal extrahepatic duct, MRI is unlikely to add any further information over and above CT.

*Strength of recommendation: MODERATE*
*Quality of evidence: LOW*

**Recommendation 10:** ^18^FDG-PET CT for detection of nodal and distant metastatic disease is recommended as part of staging investigations.

*Strength of recommendation: STRONG*
*Quality of evidence: MODERATE*

**Recommendation 11:** US or CT-guided biopsy of the primary intrahepatic tumour or metastatic lesions should be undertaken to acquire a pathological diagnosis following MDT discussion and consensus.

*Strength of recommendation: STRONG*
*Quality of evidence: HIGH*

In the diagnosis and staging of suspected CCA, the local tumour extent, vascular/biliary involvement, anatomic variations of the vessels/biliary tree and presence or absence of extrahepatic disease should be assessed. A multimodality approach is often required to combine the advantages of the various imaging techniques, which provide additive information.54-56

Imaging studies should be performed before any biliary intervention to avoid secondary inflammatory change that can mask the tumour and lead to overestimation or underestimation of its true extent.56 All imaging modalities can underestimate the longitudinal tumour extent owing to microscopic spread along the mucosal/submucosal layer of the bile duct.37

**Transabdominal ultrasound (TUS)**

Cholangiocarcinoma should be suspected when there is biliary ductal dilatation, particularly with a related mass and consistent clinical history. In suspected biliary obstruction, TUS is reliable for excluding gallstones but is operator-dependent and is insufficient alone for investigating suspected CCA. For detecting advanced CCA in patients with PSC, TUS offers specificity and negative predictive value of 90%, but sensitivity and positive predictive value are only 50%.58 59 TUS may miss small tumours and cannot accurately define tumour extent.38 60 The role of contrast enhanced ultrasound (CEUS) in CCA is also limited but might be helpful as an additional modality when assessing indeterminate focal liver lesions.

**Contrast enhanced computed tomography (CECT)**

Contrast enhanced computed tomography (CECT) should be performed in all cases of suspected CCA as the initial standard imaging modality, to include the chest, abdomen and pelvis. The main advantage is the excellent spatial resolution, providing comprehensive assessment of the primary tumour, its local vascular relationships (including any aberrant vessels) and overall resectability.55 61 62 It also allows detection of local lymphadenopathy and metastatic disease, although sensitivity is lower than that of PET.63 A meta-analysis including 448 patients from 16 studies, found data primarily related to CT, with accuracy estimates for CT evaluation of the extent of ductal tumour to be 86%; the sensitivity and specificity estimates were 89% and 92% for evaluation of portal vein involvement, 83% and 93% for hepatic artery involvement, and 61% and 88% for lymph node involvement, respectively.54

A multiphase examination of the abdomen including an unenhanced, arterial and portal venous phase is ideal. The unenhanced phase helping to differentiate high-attenuation calcified stones from enhancing tumour. Multplanar reconstruction should be routinely used.64 Assessment of vascular involvement on CT is more difficult for the hepatic artery than the portal vein, with variable positive predictive values reported for the former ranging from 53% to 95%.56 65 66 Assessment of the extent of biliary involvement can also be difficult with CT, particularly the proximal extent of perihilar tumours.

**Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP)**

A meta-analysis of 32 studies with 1626 patients reported a pooled sensitivity and specificity of MRI for T-stage of 0.90 and 0.84, and pooled sensitivity and specificity for N-stage of 0.64 and 0.69, respectively.67 In a recent study of 334 patients comparing CT and MRI staging of mass-forming intrahepatic CCA, MRI showed superior sensitivity for T-staging, with CT and MRI having comparable sensitivity for N-stage.68

The choice of contrast agent depends on tumour type and location. For mass forming iCCA, MRI with hepatobiliary contrast is reported to be the most accurate modality for identification of satellite lesions and intrahepatic metastases.69 70 Gadobenate acid-enhanced MRI (Primovist in Europe/Eovist in the United States) provides better diagnostic performance and may even give prognostic information.5 On the contrary, for intraductal, periductal and perihilar tumours, particularly if there is biliary obstruction, it is recommended that extracellular contrast agents are used.37 62

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**Box 3 Benign diseases which can mimic cholangiocarcinoma**

- Recurrent pyogenic cholangitis
- Mirizzi syndrome
- Stricture in primary sclerosing cholangitis
- Portal hypertensive biliaryopathy
- Heterotopic tissue
- Ischaemic cholangiopathy
- Inflammatory-infiltrative
- Inflammatory pseudotumour
- IgG4 sclerosing cholangitis
- Eosinophilic cholangiopathy
- Mast cell cholangiopathy
- Follicular cholangitis
- Xanthogranulomatous cholangitis
- Sarcoidosis
- Predisposition syndrome for example, Li-Fraumeni, Lynch syndrome and Peutz Jeghers, (7) people who meet diagnostic criteria for familial genetic syndromes.
**Guideline**

### Table 3  Recommendations for the use of 18F-FDG-PET for diagnosis of the primary tumour in the absence of other disease sites or pathological confirmation

<table>
<thead>
<tr>
<th>Tumour diagnosis/T-staging</th>
<th>Recommended</th>
<th>Not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodal status/N-staging</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Metastatic status/M-staging</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Relapse/recurrence (R)</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

The sensitivity and specificity of 18F-FDG-PET for T was 91.7% (95% CI 89.8% to 93.2%) and 51.3% (95% CI 46.4% to 56.2%), respectively. For N, sensitivity was 88.4% (95% CI 82.6% to 92.8%) and specificity was 69.1% (95% CI 63.8% to 74.1%). For M, sensitivity was 85.4% (95% CI 79.5% to 90.2%) and specificity was 89.7% (95% CI 86.0% to 92.7%). For R, sensitivity was 90.1% (95% CI 84.4% to 94.3%) and specificity was 83.5% (95% CI 74.4% to 90.4%). Adapted from (10).

18F-fluorodeoxyglucose (FDG) positron emission tomography (PET): FDG PET/18F PET CT

A meta-analysis supports the incorporation of 18F-PET imaging in addition to the current standard of care imaging/diagnostic tests in CCA.61 The pooled proportion of change in management due to 18F-PET CT findings was 15% (95% CI 11 to 20); the majority due to disease upstaging. The results of the meta-analysis do not support the use of 18F-PET for diagnosis of the primary tumour in the absence of other disease sites or pathological confirmation, due to low specificity (table 3). However, 18F-PET is a useful tool for identification of malignant lymph nodes (N-stage), distant metastases (M-stage) and confirmation of disease relapse if diagnosis remains unclear following standard of care imaging. This is especially important when surgery or local treatments are being considered. The prognostic role of 18F-PET and the impact of SUV max on management require further investigation in prospective studies.

### Interventional radiology

**Biopsies**

Biopsy is mandatory for confirmation of CCA diagnosis and should be performed following MDT discussion to ensure it is required and appropriate for the proposed management plan. Percutaneous liver biopsy with image guidance (mainly in the form of TUS) is suitable for intrahepatic and, where possible, pCCA if non-operable. TUS or CT guided biopsy for diagnostic purposes can also be pursued for metastatic CCA, targeting the most accessible site. There is no evidence to support and justify the routine use of CEUS in TUS-guided biopsies of focal liver lesions because of the cost and time. CEUS guidance has a role when a second biopsy is requested owing to either an insufficient initial biopsy with necrotic material or insufficient visualisation of the focal liver lesion, which could be relevant in a small percentage of cases.

Percutaneous biliary stent drainage

In patients requiring drainage with complex hilar strictures, intent should be made for endoscopic drainage with the use of percutaneous drainage only when necessary, given not just the higher morbidity but also mortality.79

### Special considerations

**Assessing the background liver**

As part of the imaging workup in potential surgical resection and transplant candidates, additional factors can be established to help determine resectability and postoperative risks. CT or MR liver volumetric analysis can be performed, with a small remnant increasing the risk of postoperative morbidity and mortality.103-105 Functional information from gadoxetic acid–enhanced MRI has also been reported to be useful in the prediction of future remnant liver function.82 Elastography techniques can detect and quantify any underlying hepatic fibrosis and provide prognostic information about the risk of hepatic failure, but must be interpreted with caution in the presence of coexisting biliary obstruction. These emerging techniques are becoming desirable in the preoperative workup of CCA but are currently not widely practised.

### Diagnosing CCA in chronic liver disease

Chronic liver disease is a predisposing factor for the development of CCA (in addition to HCC), and less commonly combined HCC-CCA. Detection and characterisation of CCA in this setting has been addressed by the Liver Imaging Reporting and Data System (LI-RADS) version 2018.68 This system is now widely adopted and describes features of liver nodules in cirrhosis as an indicator of the probability of a particular nodule being HCC. It also describes features that are more suggestive of CCA-containing tumours. If CCA is suspected, biopsy is usually required to provide a definitive diagnosis as the treatment options and prognosis will differ considerably.

### ENDOSCOPY

**Recommendation 12:** Before undertaking any endoscopic investigations for a suspected CCA, all patients should have undergone a triple-phase CT scan of the abdomen/pelvis and chest along with dynamic MRI and MRCP if proximal biliary obstruction is suspected.

*Strength of recommendation: STRONG
Quality of evidence: MODERATE*

**Recommendation 13:** Patients with operable DMTO should undergo a combination of endoscopic US and ERCP to try to confirm a malignant histological diagnosis before proceeding to surgery.

*Strength of recommendation: MODERATE
Quality of evidence: LOW*

**Recommendation 14:** In a suspected case of operable distal CCA, in the absence of jaundice, a standalone EUS should be undertaken first, to avoid the complications of ERCP, which could delay or render the patient inoperable.

*Strength of recommendation: WEAK
Quality of evidence: LOW*

**Recommendation 15:** In the presence of jaundice and DMTO, where EUS is not available, patients may only be able to have an ERCP and brush cytology in the first instance to confirm the presence of a CCA.

*Strength of recommendation: MODERATE
Quality of evidence: MODERATE*

The role of endoscopy in the management of patients with CCA is essentially for three purposes: (1) to establish a tissue/
cytological diagnosis, (2) to facilitate surgery and chemotherapy, (3) to palliate for jaundice and improve quality of life. In reference to endoscopic management this particularly applies to the management of dCCA and pCCA causing distal malignant tract obstruction (DMTO) and proximal malignant tract obstruction (PMTO), respectively, in both operable and inoperable settings.

Given that complications could arise from endoscopic procedures, that might affect the interpretation, sensitivity and specificity of the radiological staging, these guidelines advocate that primary diagnostic and staging imaging for DMTO and PMTO are undertaken beforehand. This will also facilitate endoscopic planning for the operator.

**Endoscopic standards for potentially operative distal CCA causing DMTO**

In reality, the separation of potential causes of DMTO are not always possible following central MDT review of imaging (ie, differentiating between distal CCA, pancreatic carcinoma, ampullary cancer and periampullary cancer). In this clinical scenario the first endoscopic objective is to establish the presence of malignant histology/cytology to allow the patient to proceed to Whipple’s resection with a confirmed cancer diagnosis if operable.

For dCCA—that is, a distal malignant stricture, where the objective is to drain jaundice and acquire a pathological malignant diagnosis, a combination of linear EUS fine needle biopsy (FNB) fine needle aspiration (FNA) and ERCP-directed trans papillary brushings and stenting should be undertaken. At the time of ERCP, it may be considered that bile be sent for biliary culture to guide antibiotic treatment in the postoperative period. For suspected ampullary lesions, a side viewing duodenoscopy with surface biopsies should establish the diagnosis and be considered the first-line investigation if suspected from the primary imaging. The advantage of doing a combined EUS with ERCP is that it will allow complete local assessment of pathological local lymph nodes (with follow on nodal sampling) intraductal metastases and a distal bile duct associated mass (followed by a EUS FNB/FNA of the distal bile duct mass or wall of the stricture), allowing the correct cause of MBTO to be determined. At EUS samples should be placed directly into formalin, as the benefit of onsite pathology cannot be justified in terms of time and expense.

In non-jaundiced patients with a distal biliary stricture and suspicion of MBTO, linear EUS should be undertaken, followed by review of that result by a MDT to determine if an ERCP is required to try to further establish the correct diagnosis. For those patients proceeding to ERCP, the simplest method of tissue sampling (available at most UK sites in the presence of jaundice with suspected DMTO) is to acquire a cytological diagnosis using biliary brushings and cytological examination. However, this will of course mean that the bile duct is entered putting the patient at risk of both cholangitis and pancreatitis, however, this will of course mean that the bile duct is entered putting the patient at risk of both cholangitis and pancreatitis, although some studies suggest that this might not be a major concern. For visual impression, a previous meta-analysis involving eight studies and 335 patients demonstrated a sensitivity of 90% with a specificity of 80%. For targeted tissue biopsies, a meta-analysis of 10 studies involving 456 patients showed that the sensitivity of cholangioscopy was 60% with a specificity of 98%.

EUS biopsy is not recommended for proximal strictures and masses that are potentially operable, owing to potential peritoneal seeding, although some studies suggest that this might not be a major concern. Confocal laser endomicroscopy, using the Miami and Paris classifications, remains a research tool.

**Recommendation 16: At present biliary biomarkers cannot be recommended as a replacement for cytological and histological standards. However, biliary next-generation sequencing shows great promise and should be taken forward for replicative research.**

**NIHR/UKRI funded multisite studies.**

**Strength of recommendation:** MODERATE

**Quality of evidence:** MODERATE

At present, a growing number of biliary molecular markers might add to the ability to differentiate malignant from benign biliary strictures. At present none of these can be recommended as they are often based on a range of pathologies (and varying clinical stages) and are often limited to single-centre studies. Furthermore, none at present provide near 100% sensitivity or specificity, and therefore biliary molecular markers should still be considered a research tool. However, recent publications on next-generation sequencing of bile samples have shown great promise, but until this has been validated and standardised at national laboratories with precision, accuracy and in accordance with UK laboratory accreditation processes, this technique cannot be recommended.

In conclusion, the accuracy of cytological and histological analysis is not perfect currently. In those cases, in which clinical findings cannot completely rule out the possibility of malignancy, the decision to proceed to either surgical resection or strict observation should be discussed fully with both the patient and their family, who should have a clear voice in what approach is being taken in conjunction with the MDT consensus view.

**Recommendation 17: It should be realised that the determination of a cytological/histological confirmation of MBTO is imperfect at present, and in cases where uncertainty remains, a decision on follow-up imaging versus surgery for a definitive diagnosis should be reached only after a full discussion between the patient and the clinician. These guidelines acknowledge that it is acceptable to offer surgery where histological confirmation...**
cannot exclude malignancy with absolute certainty and surgery might provide a cure and a secure diagnosis.

Strength of recommendation: STRONG
Quality of evidence: LOW

Recommendation 18: The decision to drain preoperative jaundice in distal CCA causing DMTO should be made in accordance with local HPB guidance. In cases where rapid access to surgery can be offered, it may be appropriate to bypass biliary drainage at ERCP to avoid ERCP-related complications and postoperative sepsis.

Strength of recommendation: STRONG
Quality of evidence: HIGH

Historically it was considered that drainage of preoperative hyperbilirubinaemia improves surgical outcome for distal malignant biliary obstruction. However, studies suggest an increase in postoperative complications in those patients who have undergone preoperative biliary drainage. Therefore, at present, guidance has suggested that perhaps there is a threshold level of hyperbilirubinaemia at which biliary drainage should be considered, with a threshold of 250 μmol/L being the cut-off point. However, patients with intractable pruritus, cholangitis and organ dysfunction are likely to benefit from preoperative biliary drainage with lower levels of obstructive hyperbilirubinaemia. The decision therefore not to drain DMTO before surgery implies that preoperative histological confirmation might not be achieved. Ultimately, this careful balance of decisions should be made at an HPB MDT meeting prior to any planned intervention, after all radiological imaging has been obtained along with full patient discussion.

If drainage is considered, ERCP should be performed with the placement of a fully covered metal stent for DMTO; or one or more plastic stents for PMTO, if there is an expected delay in surgery more than 4 weeks. After ERCP, cholangitis, pancreatitis, cystic duct obstruction and cholecystitis are potential risks.

Inoperable distal CCA causing DMTO

Recommendation 19: Patients with DMTO with inoperable disease from distal CCA should undergo an EUS/ERCP or stand-alone ERCP to confirm a pathological diagnosis and have their jaundice palliated.

Strength of recommendation: STRONG
Quality of evidence: HIGH

Recommendation 20: Patients with DMTO from distal CCA should have a fully covered self-expanding metal stent placed. Plastic stents should not be placed for long-term palliation of jaundice.

Strength of recommendation: STRONG
Quality of evidence: HIGH

Recommendation 21: Where patients cannot have a stent placed at ERCP, we recommend EUS guided biliary drainage is undertaken rather than PTC. However, PTC can be offered if EUS bile duct drainage is not locally available.

Strength of recommendation: STRONG
Quality of evidence: HIGH

In the case of inoperable dCCA causing obstructive jaundice, proceeding to a combined EUS and ERCP or ERCP alone, to make a simultaneous pathological diagnosis along with establishing biliary drainage is recommended. This is vital, because once a metal stent is placed, obtaining a pathological diagnosis can be extremely challenging in the case of dCCA. However, discussions about coexisting comorbidities and the degree of disease need to be strongly considered before endoscopic procedures are undertaken, as palliative care might be more appropriate for some patients in this clinical setting with very poor performance status.

The goals of drainage are to improve symptoms associated with biliary obstruction and the patient’s quality of life, in addition to facilitating the start of palliative chemotherapy by reducing the degree of jaundice. At present choices available for drainage include: ERCP, EUS guided drainage, PTC and surgical bypass. The application of endobiliary radiofrequency ablation (RFA) at the same time is at present not approved by the National Institute for Health and Care Excellence (NICE).

Endoscopic stent placement is the preferred first-line intervention due to its improved morbidity and mortality compared with surgical bypass (elevated 30-day mortality – 16.3% vs 9.6%). At present, a choice of two stents can be considered: self-expandable metallic stents (SEMS) and plastic stents. These guidelines endorse the use of fully covered SEMS given the lower rates of stent dysfunction (21.6% vs 46.8%), lower reintervention rates and better survival rates over plastic stents. Furthermore, for distal obstruction one would use fully covered SEMS rather than uncovered SEMS, which is supported by meta-analysis, despite the small risk of cystic duct obstruction.

When biliary access is not achievable at ERCP, alternative options include either EUS guided biliary drainage or PTC. Although the former has a lower complication rate, the choice of modality will probably be driven by local availability in the UK, alongside MDT discussion.

Operable perihilar CCA causing PMTO

Recommendation 22: No patient with perihilar CCA should undergo endotheraphy until the case has been fully discussed at an HPB treatment centre.

Strength of recommendation: STRONG
Quality of evidence: LOW

Recommendation 23: Unilateral drainage in the future remnant lobe should be considered ahead of surgery. Bilateral/ further stenting should only be considered if the level of preoperative jaundice does not improve, or there is cholangitis in residual obstructed biliary segments.

Strength of recommendation: MODERATE
Quality of evidence: MODERATE

The priority in the management of pCCA is to first ensure that all imaging and clinical review has been undertaken. No patient should have biliary intervention done before the case has been fully discussed at an HPB MDT meeting where a clear plan is made of what is to be achieved and operability assessed. The standard surgical treatment for pCCA is bile duct resection combined with extended hepectomy. In order to achieve this, planning of preoperative biliary drainage and/or portal vein embolisation aimed at improving the function of the future remnant liver function will be needed. For biliary drainage, particular attention needs to be given to the level of the PMTO, as determined by the Bismuth Corlette classification of biliary obstruction (figure 2).

For tissue acquisition in operable candidates, EUS is used to confirm the presence of a ductal mass/hilar mass and to take a sample of an involved locoregional/metastatic lymph node to assist in TNM staging. The ductal/hilar mass should not be sampled as this may cause peritoneal contamination and risk causing malignant cell seeding.

For PMTO, three different kinds of preoperative biliary drainage procedures can be considered: percutaneous transhepatic biliary drainage, endoscopic nasobiliary drainage and endoscopic stenting. No clinical trials have been performed...
and exclude benign hilar stricturing. Ductal biopsies to confirm malignant histology in perihilar CCA will be required. Percutaneous transhepatic biliary drainage procedures. A recent randomised controlled trial was halted early owing to a high complication rate in the PTC arm, which might suggest a benefit for ERCP. Furthermore, concurrent spyglass cholangioscopy can be offered with histological sampling. Complications of PTC and ERCP both include postprocedure related cholangitis, cholecystitis and pancreatitis. In these clinical settings repeat imaging, blood cultures/antibiotics and catheter re-assessment will be required.

Recommendation 24: Inoperable perihilar CCA - proximal malignant tract obstruction (PMTO) and jaundice should be considered for palliative stenting by either ERCP or PTC. Decisions about UL versus BL stenting should be predetermined by the local MDT depending on both local availability and expertise. 

Recommendation 25: At present the use of adjunctive endobiliary RFA and photodynamic therapy is not considered standard of care for patients with hilar and distal CCA receiving palliative care.

Recommendation 26: EUS guided biliary drainage is recognised as a potential treatment option – but use of this technique should be planned at a MDT meeting with units adopting this approach able to show clear audit data in relation to alternative and more traditional methods of biliary drainage.
Table 4 Causes of recurrent biliary obstruction

<table>
<thead>
<tr>
<th>Cause</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue ingrowth/mucosal</td>
<td>Growth of cancer or hyperplastic mucosa into the lumen of SEMS</td>
</tr>
<tr>
<td>Tissue overgrowth</td>
<td>Tumour or tissue growth beyond the ends of SEMS</td>
</tr>
<tr>
<td>Sludge, hemobilia and food</td>
<td>Occlusion of stent lumen by biliary sludge accumulation, clots and food impaction</td>
</tr>
<tr>
<td>impaction</td>
<td>Obstruction at a proximal or distal end of SEMS due to an angulated bile duct</td>
</tr>
<tr>
<td>Bile duct kinking</td>
<td>Obstruction of stent lumen due to sharp bending of a SEMS because of an angulated bile duct or tumour growth</td>
</tr>
<tr>
<td>Stent kinking</td>
<td>Obstruction of stent lumen due to sharp bending of a SEMS because of an angulated bile duct or tumour growth</td>
</tr>
</tbody>
</table>

SEMS, self-expandable metallic stents.

SURGERY FOR PERIHILAR AND INTRAHEPATIC CHOLANGIOCARCINOMA

Recommendation 29: High-resolution cross-sectional imaging is essential for assessment of resectability and accurate staging.

Strength of recommendation: STRONG
Quality of evidence: HIGH

Recommendation 30: Pre-operative preparation, including augmentation of the FLR and biliary drainage, may be required to ensure safe resection.

Strength of recommendation: STRONG
Quality of evidence: HIGH

Recommendation 31: Staging laparoscopy should be used selectively.

Strength of recommendation: STRONG
Quality of evidence: MODERATE

Recommendation 32: R0 resection is the only curative treatment available.

Strength of recommendation: STRONG
Quality of evidence: MODERATE

Recommendation 33: Surgical resection of CCA should be undertaken only at high-volume centres with expertise across all relevant supporting specialties, including interventional radiology, endoscopy, hepatobiliary medicine, oncology and pathology.

Strength of recommendation: STRONG
Quality of evidence: MODERATE

Surgical resection is the only therapeutic option (other than liver transplantation for a small proportion of selected patients [see section on liver transplantation, and possibly ablation for small iCCA] that offers a potential cure for CCA.

Surgical approaches have become increasingly aggressive over the past decade with the express aim of obtaining complete tumour excision (R0) while maintaining adequate blood supply, biliary drainage and sufficient functional liver remnant (FLR) for patients to recover successfully. Distal CCA is treated with a Whipple’s resection and will not be focused on further as the surgical management of pancreatic ductal adenocarcinoma is already well described in international guidelines. For pCCA, bile duct excision, partial hepectommy and en bloc caudate lobectomy are frequently required to achieve negative margins. For iCCA, a complete (R0) resection with an adequate liver remnant is the preferred surgical treatment. These challenging procedures are associated with significant morbidity and in-hospital mortality (up to 15%) and should only be undertaken in high-volume centres with the expertise required to manage such patients.

In 2007, DeOliveira et al reported on 564 CCA resections, from a single centre. The average size of iCCA was 5.5 cm compared with 2.5 cm for pCCA and 2 cm for dCCA. Furthermore, despite the distinct macroscopic morphological subtypes, CCA uniformly spreads with perineural (intrahepatic 39%; perihilar and distal 75 %), lymphatic (intrahepatic 61%; perihilar 50%; distal 73 %) and vascular invasion (intrahepatic 64%; perihilar 38%; distal 73%). These factors often influence the surgical decision-making and outcome.

Determining resectability

This is an essential part of any surgical strategy and is reliant on high-quality imaging and accurate staging.

Staging systems and classification

iCCA staging follows the TNM staging model for epithelial tumours and lymph node metastases, and extrapancreatic metastases are much more likely than HCC. Current staging classifications (including: AJCC/UICC system (8th edition) and the Okabayashi system) use variables such as tumour size (>5 cm), multifocal and bilateral tumours and vascular invasion (micro and/or macro) as prognostic determinants. (see online supplemental figure 1). Significant changes have been made in the 8th edition of the AJCC staging of intrahepatic CCA. A tumour size cut-off point of 5 cm now separates the T1 category into T1a and T1b subgroups. This is because a tumour diameter >5 cm is an independent prognostic factor for overall survival and is also associated with a higher chance of microscopic vascular invasion and higher tumour grade. T2 tumours are now no longer subdivided into T2a and T2b because of the equivalent prognostic effect of vascular invasion and multifocal disease. T3 tumours are now defined as invading the visceral peritoneum (an area of controversy), while T4 are tumours involving local extrapancreatic structures by direct invasion and are categorised as stage IIIb.
Staging systems and classification

A problem with TNM staging for pCCA is that a small, badly place tumour markedly worsens prognosis, and T staging is inadequate. Current staging classifications include: the Memorial Sloan-Kettering Cancer Centre (MSKCC) system, the AJCC system (8th edition) (see online supplemental figures 2 and 3) and the modified Bismuth-Corlette (BC) classification (used to anatomically locate the tumour with reference to the bifurcation of the common hepatic duct). Important features common to all systems include: hepatic duct involvement (unilateral vs bilateral) and portal vein involvement (ipsilateral vs contralateral vs main). Other variables include: ipsilateral hepatic hemi-atrophy, tumour extension into second-order biliary radicles, tumour extension into surrounding adipose tissue or hepatic parenchyma, hepatic artery involvement (ipsilateral vs contralateral vs common hepatic artery), regional lymph node metastases.

Assessment of resectability using the BC classification system is helpful in anatomically locating the tumour with reference to the bifurcation of the common hepatic duct (CHD) (figure 2). Tumours located distally in the biliary tree to the CHD are classified as BC type 1 tumours. Tumours located proximal to the CHD in the biliary tree are further divided into four types. The BC classification is broadly used to describe the longitudinal extension of the tumour from the CHD. Type 2 BC tumours are inclusive of the CHD, type 3a BC tumours incorporate longitudinal extension along the right hepatic main duct, and type 3b BC tumours incorporate extension along the left hepatic main duct exclusively. Type 4 BC tumour classification incorporates biductal extension and multifocal ductal disease.

While the BC system has been universally adopted as an anatomical descriptive system for tumour location, it is poor at accurately describing longitudinal extension and is commensurately poor at distinguishing between left and right duct extension. The BC system has been shown to have a limited usefulness in determining contraindications to surgical approach and has no evidence-based role with respect to postresection prognosis.

The MSKCC staging system attempts to account for both longitudinal and radial extension of the primary tumour (figure 3) and is yet to be robustly validated in an external modern cohort for resectability. The majority of validation studies are concerned with determining the usefulness of the system with reference to survival.

Unresectability can result from either extensive local disease (including vascular and nodal involvement), presence of distant metastases or comorbidity of the patient. Local unresectability can be due to involvement of the portal vein and hepatic artery on the side of the future remnant liver without the possibility of a vascular reconstruction, extensive bilateral proximal infiltration of the tumour into secondary biliary radicles (segmental bile ducts) and/or massive extension of tumour into the liver parenchyma. Furthermore, extrapancreatic metastases including distant lymph node metastases beyond the hepatoduodenal ligament (N2 nodes), are associated with poor survival and in most centres, are considered as unresectable disease.

Staging laparoscopy

The usefulness of routine staging laparoscopy (SL) in stratifying patients for resection remains controversial. A meta-analysis by the Amsterdam Medical Centre (AMC) hepatobiliary group suggests that SL in modern cohorts has limited usefulness owing to the improved sensitivity of multislice CT and PET-CT in determining the presence of peritoneal and distant metastases. The MSKCC group advocate selected use of SL for locally advanced MSKCC stage T2 or T3 patients. This approach risks understaging small surgically resectable tumours that have already spread in the peritoneum beyond the surgical field. The yields of SL for peritoneal disease vary between 10% and 17% of all patients undergoing surgical assessment, precluding unnecessary laparotomy in this group. Laparoscopic ultrasound may provide additional information for determining hilar resectability, particularly with respect to defining radial extension into surrounding vascular structures; however, its usefulness has yet to be demonstrated in a large modern cohort. The risk of occult metastatic disease is particularly high in patients with high serum CA 19–9, major vascular invasion and suspicious lymph nodes. Exploratory laparotomy without resection should be avoided because it delays palliative systemic chemotherapy.

Functional liver remnant (FLR)

Ensuring an adequate functional liver remnant (FLR) is essential for safe resection. This can be determined preoperatively by the use of CT volumetry, which determines the ratio of FLR to non-tumourous liver volume. The non-tumourous liver volume can be determined either by direct CT measurement or by estimation of body surface area. Ribero et al demonstrated, in a large modern cohort of 243 patients, that CT measurement underestimated the risk of hepatic insufficiency postoperatively and that body surface assessments were more accurate in determining subsequent risk. Augmentation of the FLR to reduce the likelihood of post-resection liver insufficiency has become a widely accepted technique. Augmentation typically is used in patients with right-sided intrahepatic or hilar CCA type 3A (Bismuth-Corlette staging, figure 2). FLR augmentation is typically undertaken on patients for whom the FLR post-resection would be 20% in patients with normal liver parenchyma, 30% in post neoadjuvant chemotherapy (a rare cohort in patients with CCA); 40% in patients with established liver cirrhosis. The main approaches to augmentation are portal vein embolisation (PVE); portal vein ligation (PVL); and associated liver partition and portal vein ligation (ALPPS).

FLR responsiveness to PVE has been demonstrated to be an independent preoperative predictor of postoperative liver insufficiency. PVL and ALPPS are surgical procedures used to produce FLR hypertrophy. PVL involves surgical ligation of the portal vein to ensure redirection of portal venous blood flow.
ALPPS is a novel concept with a narrow evidence base and significant controversy. The procedure involves surgical splitting of the hepatic parenchyma and ligation of the right portal vein to provide complete partition and reduce the chance of collateralisation of blood supply to the FLR.\textsuperscript{159,160} Following the initial stage of vascular ligation and parenchymal microvascular isolation, a second stage right trisectionectomy is undertaken for resection of the primary tumour, following radiographically demonstrated adequate FLR hypertrophy.\textsuperscript{161} The rate of growth of the FLR is also significantly faster, with maximal growth occurring at day 9 postoperatively compared with 4–6 weeks after PVE.\textsuperscript{160,162} The short interval between the initial portal vein ligation and parenchymal transection and the peak hypertrophic stage potentially increases the likelihood of completion of the second stage of the procedure, the trisectionectomy. PVE and two-stage hepatectomy require significant periods between the initial procedure and completing the resection of the primary tumour.\textsuperscript{163} This interval produces a potential for disease progression, thereby precluding completion of resection. Laparoscopic approaches to ALPPS have also been reported demonstrating the feasibility of the procedure to be adopted as a minimally invasive approach for hypertrophy of the FLR.\textsuperscript{164–167} Although there was initial support for the use of this approach for FLR growth, data from the international ALPPS Registry has demonstrated that this technique, when used for perihilar cholangiocarcinoma is associated with exceptional mortality of 48%. Hence this technique is not currently recommended in this clinical setting.\textsuperscript{168}

**Preoperative biliary drainage**

There is clear consensus that preoperative biliary decompression is indicated in patients with cholangitis, patients undergoing preoperative antineoplastic therapy, patients with hyperbilirubinaemia-induced malnutrition, hepatic insufficiency or renal insufficiency, and patients undergoing PVE. Although some authors have advocated no preoperative biliary decompression in patients with adequate nutritional status and no cholangitis, others, especially those from centres in Asia, have advocated biliary drainage as mandatory, regardless of bilirubin level, because of the association between cholangitis and outcome.\textsuperscript{169} Decompression of the bile duct can be facilitated with either PTC or ERCP (see recommendations 23/24). In addition to the reduction of both procedural risks and need for re-intervention with ERCP, PTC catheters can provide much better delineation of the extent of the spread of endobiliary tumour within the liver for resection planning.\textsuperscript{170,171} Even though endoscopic drainage is highly successful, complex lesions may not respond adequately to endobiliary drainage and hence, particularly in patients who may be candidates for resection, the care team should not hesitate to establish durable biliary drainage with percutaneous catheters if required.\textsuperscript{172}

**Intraoperative surgical considerations**

**Resection of iCCA**

A complete (R0) resection with an adequate liver remnant is the preferred surgical treatment. Most patients have a single large tumour requiring a (extended) hemi-hepatectomy. If the FLR volume is below 30% enhancement of the FLR is required (see section on FLR). ALPPS can be considered if the remnant volume remains inadequate after PVE or if intraoperatively a larger resection than expected is needed on imaging.\textsuperscript{173}

About 15% of patients with CCA who undergo a resection present with biliary obstruction. Most of these patients will require preoperative biliary drainage, in particular in the setting of cholangitis or a small FLR (see also section on biliary drainage in the first part on pCCA). Resection without biliary drainage can be considered if the future liver remnant exceeds 50%. Resection of the biliary confluence is typically needed in patients with biliary obstruction, followed by a Roux-en-Y hepaticojejunostomy.\textsuperscript{174} Current guidelines recommend performing a lymphadenectomy in all patients with resectable iCCA.\textsuperscript{177,178}

Most patients with iCCA (75%) will require an (extended) hemi-hepatectomy with higher than 1% mortality. Mortality is higher when vascular reconstructions are needed, and for patients with cirrhosis who are operated on.\textsuperscript{179} The majority of patients will develop recurrent disease after resection of iCCA. In a large study by Hyder et al, the median recurrence-free survival of 301 patients was 20 months. Most patients developed an initial intrahepatic recurrence (61%). An initial extrahepatic recurrence was found in 21%, and 19% had a simultaneous intrahepatic and extrahepatic recurrence.\textsuperscript{174} The median overall survival after a curative resection is about 30 months with a 5-year overall survival of approximately 30%–40% based on several large series.\textsuperscript{177}

**Locoregional treatments**

Surgical resection is the preferred treatment for resectable iCCA. Lesions of less than 3 cm located centrally in the liver may be considered for thermal ablation (such as radiofrequency or microwave ablation) especially those lesions in patients with a high surgical risk (eg, cirrhosis). The main disadvantage of thermal ablation is an increased risk of local recurrence and the inability to perform a lymphadenectomy, although nodal metastasis is unlikely in small lesions, and removing positive lymph nodes has not been shown to improve survival. In lesions too large for thermal ablation, transarterial treatments are available, such as transarterial chemoembolisation, elective internal radiation therapy with Y-90 and hepatic arterial infusion chemotherapy.\textsuperscript{178,179}

**pCCA**

Exploratory laparotomy is undertaken following exclusion of disseminated intraperitoneal disease at SL. R0 resection of the primary tumour confers significant survival benefits compared with R1/R2 resection.\textsuperscript{180} The focus of exploratory laparotomy is to determine and confirm local resectability of the primary tumour with regards to local vascular invasion, distal biliary duct extension, and intra-abdominal nodal spread. Surgical assessment of vascular invasion includes visual inspection and palpation, with intraoperative ultrasound providing evaluation of extension of the tumour into the hilar vascular structures. Coeliac axis nodes confirmed intraoperatively on frozen section are considered to represent metastatic disease outside of the surgical field and, if detected, would constitute closure without proceeding to resection.

Distal bile duct transection occurs early in the resection to ensure adequate access to the hilar vasculature structures. During isolation and transection of the distal margin, the specimen routinely undergoes frozen section analysis. Frozen section analysis is used to determine the presence of microscopic disease at the distal resection margin. If there appears to be microscopic invasive disease threatening the resection margin then further excision can be undertaken to ensure adequate R0 resection margins. Patients undergoing re-excision of the distal margin and subsequently achieving a negative frozen section of the new margin appear to have similar survival characteristics to patients who achieved negative margins on the initial frozen section.\textsuperscript{181}
Carcinoma in situ threatening or present at the resection margin does not appear to produce negative effects on survival and can essentially be considered as being equivalent to a negative frozen section result. 182 Frozen section has a sensitivity of between 60% and 70%, with a significant number of false-negative and false-positive findings confirmed on subsequent full histopathological assessment. 183-184 The false-negative results have been putatively linked to the use of preoperative biliary stenting producing epithelial regeneration at the site of the distal margin. 185 Regeneration of the normal epithelial layer occurs in response to the friction produced by the stent at this site. Following confirmation of clear distal margins on frozen section attempted resection of the primary tumour can proceed. Some centres collect bile swabs during hilar CCA resections to guide subsequent antibiotic use.

Traditionally, concomitant resection of the caudate lobe is undertaken due to the high proportion of patients with microscopic infiltration of the caudate lobe. 186-187 Sufficient resection to achieve R0 resection margins is advocated. 188-189 Extended right hemi-hepatectomy, inclusive of the inferior section of segment 4 (4B) with hilar bile duct excision at the confluence, has been demonstrated to achieve good R0 resection margins for type 3a disease. 190 The anatomical proximity of the portal vein to the hilar confluence has led to the development of en bloc ‘no-touch’ techniques including resection of the portal vein as necessary. 191 En bloc resection has been suggested to offer improved survival, but may also be associated with increased perioperative mortality. 192-193

Right-sided trisectionectomy is the preferred approach, if feasible, for resecting hilar CCA. Left-sided approaches for hilar pathology are surgically demanding and reserved solely for predominantly left-sided BC 3b tumours. 194 Principally, the difficulty of the approach relates to the extrahepatic course of the respective portal vein. The right portal vein has a short extrahepatic course, which makes reconstruction of the portal vein following left-sided resection difficult. 194-196 Left-sided resections for BC 3b tumours are also more likely to involve complex hepatic arterial resection and reconstruction. The right hepatic artery is potentially threatened due to its proximity to the left portal vein and its course within the hilum. 197 Consequently, there is a corresponding increase in potential for postoperative liver insufficiency if the right hepatic artery is encountered during a left-sided resection.

Invasion of the portal vein is reflective of locally advanced CCA and represents T3/T4 disease. Despite portal vein invasion representing more locally advanced disease, overall survival in allcomers undergoing resection is comparable to that of patients undergoing major hepatectomy without portal vein resection. 180-188 Vascular resection and reconstruction of the hepatic artery, which appears to confer limited survival benefits in highly selected patients, may be suitable. 199 200

An important resection consideration is ensuring that an adequate lymphadenectomy field is achieved. Fastidious dissection of the course of the proper hepatic and common hepatic artery, in the hepatoduodenal ligament, to the level eight lymph node in the retroperitoneum is required to gain an adequate surgical field. Acquisition of lymphatic tissue is technically difficult to achieve and has substantial risk of comorbidity to the patient. Inadequate acquisition of lymphatic tissue, with fewer than five nodes resected, has a detrimental effect on overall survival due to understaging of disease. 201 Acquisition of 15 lymph nodes within the resection specimen has been suggested as the optimal lymphadenectomy for accurate staging of disease and subsequent determination of prognosis. 202 However, the optimal number of lymph nodes acquired within the resection specimen rarely reaches this number, with the median number of nodes acquired being between 5 and 10. 203-205 The ratio of positive lymph nodes to total lymph nodes acquired has been linked to overall survival and recurrence-free survival. 206 207

**Postoperative prognostic factors and follow-up**

A multi-institutional series of 306 resections was used to develop a prognostic nomogram, which included margin status; lymph node positivity and tumour differentiation, which predicted disease-free survival and could facilitate stratification of patients into clinical trials (figure 4). 208 Subsequent to this, a large meta-analysis of in excess of 4500 resected patients with CCA has validated the above prognostic factors, as well as identifying a number of additional variables that have an impact on outcome (table 5). 209

Currently there is no consensus as to frequency of clinical follow-up, imaging or the use of tumour markers following resection for CCA. This lack of consensus was demonstrated in the survey undertaken by Cholangiocarcinoma-UK of NHS units undertaking this surgery. 210 However, the majority of centres undertake 6-monthly cross-sectional imaging with a CT scan of chest, abdomen and pelvis, as well as studying tumour markers for at least 2 years after resection. 210

**Impact of surgical activity on outcome**

Correlation of surgeon activity and patient outcome is challenging to quantify as there are many confounding variables—for example, expertise of support services, which can affect patient outcomes. Idrees et al using the US National Comprehensive Cancer Network database, containing in excess of 40 000 CCA resections, showed that a hospital volume of 14 operations/year was the most sensitive and specific value associated with mortality. 211 Surgery at high-volume hospitals (HR=0.92, 95% CI 0.88 to 0.97, p<0.001) was independently associated with improved overall survival. 211 Another recent study determined the annual case volume for optimum outcomes for 2471 patients with resected pCCA at 471 facilities between 2010 and 2017. They reported that centres undertaking at least seven perihilar resections a year have improved 90-day mortality and improved perioperative outcomes. 212

![Figure 4](http://gut.bmj.com)
**LIVER TRANSPLANTATION FOR CCA**

Recommendation 34: Liver transplantation for selected patients with pCCA in the presence of chronic liver disease (most commonly primary sclerosing cholangitis), less than 3 cm in size with no evidence of extrahepatic disease results in long-term disease-free survival. This is an established indication in an increasing number of centres internationally. There is a need for evaluation of novel neoadjuvant chemoradiation strategies and assessment of long-term outcomes with national protocols and multi-centre studies. Liver transplantation in the absence of background chronic liver disease remains an investigational treatment.

*Strength of recommendation: MODERATE*  
*Quality of evidence: STRONG*

Recommendation 35: Neoadjuvant therapy in uncontrolled studies appears to be effective in controlling disease and selecting patients who are most likely to benefit from transplantation.  

*Strength of recommendation: MODERATE*  
*Quality of evidence: MODERATE*

Recommendation 36: Transplantation for iCCA on a background of chronic liver disease precluding resection should be evaluated prospectively within a national protocol. LAG tumour size criteria are to be monitored and modified to improve recruitment for evaluation.  

*Strength of recommendation: STRONG*  
*Quality of evidence: MODERATE*

Although potentially curative, unfortunately liver resection is only applicable for a minority of patients due to the extent of the cancer or the presence of background chronic liver disease at presentation. Liver transplantation is a potential treatment option for selected patients with pCCA or iCCA.

**Perihilar CCA**

Initial attempts at liver transplantation for pCCA produced poor outcomes, which have been attributed to selecting patients with advanced cancers, a surgical learning curve, immunosuppression management and lack of understanding of tumour biology. Liver transplantation for pCCA was initiated with publications from Nebraska and Mayo Clinic, which introduced strict selection protocols to identify a group of patients likely to benefit from liver transplantation, and these have been adopted by other centres.

De Vreede et al published the initial Mayo experience in 2000, with 19 patients enrolled into a neoadjuvant therapy protocol. Eleven patients underwent transplantation. Of eight with long term follow-up (median 44 months), only one patient developed recurrence. Similarly, Sudan et al published the Nebraska experience in 11 patients who underwent transplantation after neoadjuvant chemoradiotherapy, with 5 of the 11 patients alive and disease free at a median follow-up of 7.5 years.

The majority of cases reported more recently have adopted the Mayo protocol with minor modifications. The key protocol components are: selection of patients, neoadjuvant therapy and test of time. Patients with localised cancers with a dominant stricture or less than 3 cm tumour were included. Intrahepatic and extrahepatic metastases including any nodal metastases are exclusion criteria. Controversially, histology or cytology was not considered essential for diagnosis of CCA. Elevated serum CA 19 9 of greater than 100 U/mL, ploidy of cells on bile cytology (FISH), or a dominant stricture associated with a mass lesion on imaging were considered sufficient for enrolment into the protocol. Prior attempt at transperitoneal biopsy (percutaneous or EUS guided) was another exclusion criterion, based on increased risk of tumour dissemination.

Neoadjuvant therapy involved external beam radiation therapy with concurrent chemotherapy (chemosensitisation), followed by brachytherapy whenever possible. Patients were then restaged and continued to receive systemic chemotherapy with oral capecitabine until the time of transplant. Over a period of 26 years (1993–2019), 376 patients including those with de novo CCA (148) were enrolled on this protocol at the Mayo clinic. Of these, 14% were excluded as they developed disease progression during neoadjuvant therapy. A further 14% of patients were excluded at staging surgery, which took place after neoadjuvant therapy because of extrahepatic metastases, and were excluded from transplant as failing the ‘test of time’ with unfavourable tumour biology.

A recent systematic review included 20 studies from 2000 until 2019, with 428 patients eligible for analysis. The pooled 1-, 3-, and 5-year overall survival rates following liver transplantation without neoadjuvant therapy (n=156) were 71.2% (95% CI 62.2% to 79.4%), 48.0% (95% CI 35.0% to 60.9%) and 31.6% (95% CI 23.1% to 40.7%), respectively. Patients who had neoadjuvant therapy prior to transplantation (n=272) had higher survival of 82.8% (95% CI 73.0% to 90.8%), 65.5% (95% CI 48.7% to 80.3%), and 65.1% (95% CI 55.1% to 74.5%) at 1, 3 and 5 years, respectively. Similarly, the recurrence rate was 51.7% in patients not undergoing neoadjuvant therapy compared with 24.1% for patients who did. Only 4 of the 20 studies reported pretransplant histological confirmation of adenocarcinoma or malignant/suspicious cells on cytology.

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**Table 5 Meta-analysis of prognostic factors**

<table>
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<th>N</th>
<th>Heterogeneity</th>
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<tr>
<td></td>
<td></td>
<td>I²</td>
<td>P value</td>
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<tr>
<td>Tumour size (small)</td>
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<td>0.470</td>
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<tr>
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</tr>
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<tr>
<td>Tumour differentiation (well differentiated)</td>
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<td>0.0%</td>
<td>0.505</td>
</tr>
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</table>

LN, lymph node.
145 liver explants from studies not using neoadjuvant therapy, malignancy was found in 142 (97.9%), compared with no evidence of malignancy in 126 (49.4%) of 255 patients who had neoadjuvant therapy. These 126 patients are presumed to have had complete pathological response to neoadjuvant therapy, although the possibility exists that in at least some of the patients there was no malignancy at all.

Patients with background PSC had better survival than patients with de novo cancers. The most recent experience from Mayo, published in 2016, demonstrates a 5-year survival of 74% for patients with background PSC compared with 58% for de novo CCA after transplantation. Response to neoadjuvant therapy is another independent predictor of outcomes. 222 Five-year disease free-survival was 93.5% in patients with complete or near-complete response to neoadjuvant therapy (<1% viable tumour in explant) compared with 51.5%, 41.6% and 27.3% for tumours with 1–10%, >10–30% and >30% viable tumour, respectively. A limitation of these data is that the prognostic assessment was histology of the explant and hence it cannot be used for case selection.

**Intrahepatic CCA**

Intrahepatic CCA, while rare, is increasingly diagnosed in patients with background chronic liver disease. Where feasible, liver resection remains the gold standard for treatment. The associated chronic liver disease and function, location of tumour and portal hypertension limit applicability of liver resection even in patients with small iCCA.

iCCA currently remains a contraindication for liver transplantation in most programmes worldwide. 223 Recent multicentre studies showing encouraging outcomes have prompted reassessment of iCCA on a background of chronic liver disease as an indication for liver transplantation. 224–230 Much of these data are retrospective, with iCCA found incidentally in the explant or being misdiagnosed as HCC radiologically. A single-centre study of 13 patients, 228 reported no recurrence in four patients with well-differentiated tumours compared with 78% recurrence in those with moderately differentiated tumours, suggesting that tumour biology may be key to transplant selection. A multi-centre study of eight patients from Spain with very early iCCA (defined as solitary tumours less than 2 cm in size) reported 73% 5-year survival. 229 An international multicentre study again demonstrated that the number and size of tumours were key factors influencing long-term outcomes. 220 Fifteen patients with very early iCCA had a 5-year 65% survival with recurrence rates comparable to those of transplant outcomes for HCC within Milan criteria. Jung et al reported the outcome of liver transplantation for 16 patients with incidental iCCA and compared their outcomes using a propensity score matched analysis with 100 patients with CCA who underwent liver resection. 231 Of patients with very early iCCA there was no recurrence following liver transplantation (n=3, follow-up of 39.1±29.9 months), whereas 23% (6/26) of those undergoing resection developed recurrence. Half of the recurrences of very early iCCA were intrahepatic, and the authors argued that these patients might have potentially benefited from transplant.

A recent multicentre French study advocates a more liberal approach towards tumour size. A retrospective three-centre study compared outcomes of patients who underwent liver transplantation with incidental iCCA found at explants (n=49) with those of patients who underwent liver resection for iCCA with background chronic liver disease (n=26). 232 The incidence of incidental iCCA and mixed hepatocellular–cholangiocarcinoma increased from 0.6% of transplants in 2002 to 2% by 2015. At a median follow-up of 25 months, the 1-, 3- and 5-year survival of patients who underwent liver transplantation was 90.76 and 67%, respectively, compared with 92.59 and 40% for patients who had resection. The recurrence-free survival was 75% at 5 years after transplantation compared with 36% for resection. Independent risk factors for recurrence were the size of the largest tumour and differentiation. The 1- and 5-year survival for tumours <2 cm after transplantation was 92.87 and 69% compared with 87.65 and 65% for tumours 2–5 cm in size. Combined HCC–CCA had similar outcomes to those of iCCA. Of patients who underwent liver transplantation, 55% had tran-sarterial chemoembolisation as bridging therapy and five patients had adjuvant chemotherapy with gemcitabine and oxaliplatin.

Two studies investigated the role of neoadjuvant therapy prior to liver transplantation for large unresectable iCCA. 233,234 Systemic therapy and locoregional approach with radioembolisation were used in these studies. These studies indicate potential benefit of neoadjuvant and adjuvant therapies, which needs to be investigated in larger clinical trials.

**SYSTEMIC THERAPY**

**Recommendation 37**: Patients who have undergone surgical resection for CCA should be considered for 24 weeks of adjuvant chemotherapy (currently capecitabine).

*Strength of recommendation: STRONG*

*Quality of evidence: MODERATE*

**Recommendation 38**: The routine use of neoadjuvant chemotherapy in patients with resectable CCA is not recommended.

*Strength of recommendation: STRONG*

*Quality of evidence: LOW*

**Recommendation 39**: CisGem chemotherapy is recommended as the first-line treatment in patients with advanced BTC. Immunotherapy may be added to CisGem chemotherapy, if approved and available, cognisant of the magnitude of benefit and toxicities.

*Strength of recommendation: STRONG*

*Quality of evidence: HIGH*

**Recommendation 40**: Combination chemotherapy is recommended in patients with adequate performance status following failure of first-line chemotherapy, particularly in the absence of a targetable molecular alteration.

*Strength of recommendation: MODERATE*

*Quality of evidence: HIGH*

**Recommendation 41**: CCA should be subjected to molecular profiling at the earliest opportunity, and results and treatment options should be reviewed by clinicians with appropriate expertise.

*Strength of recommendation: STRONG*

*Quality of evidence: HIGH*

**Adjuvant treatment**

The aim of adjuvant treatment is to reduce the chances of disease relapse, thereby improving survival, following potentially curative resection. The PRODIGE 12 randomised phase III trial failed to show benefit of gemcitabine and oxaliplatin chemotherapy in patients with resected biliary tract cancer (CCA or gallbladder cancer) over observation alone235; there was also no benefit from gemcitabine in a phase III study limited to patients with extrahepatic (perihilar and distal) CCA. 236 The STAMP study compared gemcitabine and cisplatin with capecitabine in node-positive extrahepatic CCA. This was negative, but the sample size of 101 patients was small. 237 The BILCAP phase III
Guideline

study, randomising patients with CCA and gallbladder cancer to receive adjuvant capcitabine versus observation failed to demonstrate an improvement in overall survival (the primary endpoint) by intention-to-treat analysis (HR=0.81; 95% CI 0.63 to 1.04; p=0.097). However, there was an improvement in survival according to the prespecified sensitivity analysis adjusted for sex, tumour grade and nodal stage (HR=0.71; 95% CI 0.53 to 0.92; p=0.010). This, together with the clinically meaningful numerical improvement in median survival (51.1 vs 36.4 months) favouring chemotherapy, by intention-to-treat analysis) has led to the adoption of capcitabine as standard of care and the reference for future studies.

Most recently, the results of the JCOG1202 (ASCOT) study were presented. In this phase III study patients with biliary tract cancer (CCA and gallbladder cancer) were randomised to receive S1 (an oral fluoropyrimidine) versus observation alone. There was an improvement in the 3-year overall survival (77.1% vs 67.6% in favour of S1; HR=0.694; 95% CI 0.514 to 0.935; one-sided p value 0.008), although the 3-year relapse-free survival was not statistically significantly different (62.4% vs 50.9% for S1 vs surgery, respectively, HR=0.797; 95% CI 0.613 to 1.035). Further follow-up is required as there were only 40.7% of events (deaths) at the time of the analysis. Although this supports the findings of the BILCAP study, the ASCOT study did not include a Western population and therefore capcitabine is the recommended adjuvant treatment in patients following resected biliary tract cancer.

Although there have been several phase II studies evaluating systemic treatments in the neoadjuvant setting, no phase III studies are available on which to make any high-level recommendations. However, in patients with locally advanced disease who are initially deemed unresectable and who derive a good response to systemic therapy, it is recommended that treatment of the patients is rediscussed at the appropriate MDT meeting to re-evaluate potentially curative resection.

Advanced disease

It can be difficult to obtain an unequivocal histological or cytological diagnosis in CCA, particularly perihilar CCA. At least two, and if appropriate more, attempts should be made at unequivocal histological or cytological diagnosis, and the diagnosis reconsidered if persistently negative. If there is a strong clinical suspicion of malignancy despite negative unequivocal histological or cytology, systemic therapy may be considered following discussion with the MDT and the patient. This scenario should be a rare exception.

In advanced disease, patients who do not receive systemic therapy have a very short life expectancy, typically 3–4 months. Phase III studies have shown an improvement in overall survival with chemotherapy compared with supportive care alone. The UK ABC-02 study defined the combination of cisplatin and gemcitabine (CisGem) as the standard-of-care regimen in 2009 having shown an improved survival of the doublet to single-agent gemcitabine; comparable findings were seen in the BT22 randomised phase II study. Use of gemcitabine alone in patients with poor performance status would be reasonable and substitution of oxaliplatin for cisplatin is reasonable in those with renal impairment.

Intensification of chemotherapy with triplet regimens has delivered mixed results. In the randomised phase II/III PRODIGE 38 (AMEBICA) study, the modified (m)FOLFIRINOX regimen (5-FU, irinotecan and oxaliplatin) was compared with CisGem in the first-line setting. There was no improvement in the primary endpoint of the randomised phase II stage (6-month progression-free survival: 44.6% (90% CI 35.7% to 53.7%) with mFOLFIRINOX vs 47.3% (90% CI 38.4% to 56.3%) with CisGem), and the study did not proceed to phase III. In the KHBO1401-MITSUBA study, the triplet of CisGem plus S1 showed an improvement in overall survival versus CisGem (median 13.5 vs 12.6 months; HR=0.79; 95% CI 0.63 to 0.99; p=0.046 – pending full manuscript) in favour of the triplet with additional, although manageable, toxicity rendering it as another treatment option in phase II. Based on promising activity seen in a phase II study (median progression-free survival of 11.8 months, 95% CI 6.0 to 15.6; partial response rate of 45% and disease control rate of 84%; and median overall survival of 19.2 months (95% CI 13.2 to not estimable)), the SWOG 1815 randomised phase III study compared gemcitabine and cisplatin with or without nab-paclitaxel; however, the result was was negative. As such overall survival outcomes using triplet-agent chemotherapy in biliary tract cancer have been disappointing, although response rates have improved. Triplet-agent chemotherapy may be most relevant in patients where a higher response is pivotal—for example, in rendering disease potentially resectable.

Two randomised studies have shown an improvement in overall survival in the second-line setting; ABC-06 and NIFTY. In the phase III ABC-06 study, patients were randomised to active symptom control alone or with FOLFOX (5-FU and oxaliplatin) chemotherapy. FOLFOX-treated patients had an improved overall survival (HR=0.69, 95% CI 0.50 to 0.97, p=0.031); notably survival was greater than expected in the active symptom control alone arm (5.3 vs 4 months) highlighting the need for proactive screening, identification and treatment of disease-related complications (particularly biliary obstruction and infection). In the randomised phase IIb NIFTY study, Korean patients received either 5-FU monotherapy or in combination with nano-liposomal irinotecan. Combination chemotherapy was associated with an improved progression-free survival (primary endpoint, by blinded independent central review): 7.1 months, 95% CI 3.6 to 8.8 vs 1.4 months, 95% CI 1.2 to 1.5 with monotherapy (HR=0.56, 95% CI 0.39 to 0.81, p=0.0019) as well as overall survival (HR=0.68, 95% CI 0.48 to 0.98, p=0.035). The incremental benefit of using nano-liposomal irinotecan in preference to conventional irinotecan is unknown.

Immunotherapy

A phase III study to evaluate the benefit of adding immunotherapy (durvalumab, a programmed death-ligand 1 (PD-L1) inhibitor) to first-line chemotherapy (TOPAZ-1) has shown a reduction in risk of death by 20% (HR=0.80, 95% CI 0.66 to 0.97, p=0.021). The benefit is mainly seen beyond the first 6 months of treatment, with increasing divergence of the survival curves at 12 months (54.1% vs 48% alive), 18 months (35.1% vs 25.6%) and 24 months (24.9% vs 10.4%) with little difference at the median (12.8 vs 11.5 months) for durvalumab and chemotherapy, respectively. The progression-free survival and overall response rate were also statistically significantly improved, with evidence of durable responses in some patients with no new safety concerns from the new combination. No enrichment criteria have emerged to date (PD-L1 expression did not correlate with outcome) to identify patients most likely to benefit. The KEYNOTE-966 study (cisplatin and gemcitabine with either pembrolizumab or placebo) showed very similar outcomes, confirming the first-line standard of care of cisplatin, gemcitabine and immunotherapy.
Targetable molecular alterations in biliary tract cancer

A significant proportion of biliary tract cancers have an actionable molecular alteration (Table 6). Although iCCA have the largest proportion (~50%), the other sites of CCA also have up to 30%. Some alterations are specific to anatomical subtypes—for instance, FGFR2 and a IDH1 localised iCCA while some are present throughout the whole biliary tract, for instance BRAF. Notably, these alterations are mutually exclusive to other common drivers of malignancy, notably RAS, and consequently offer opportunities for benefit from targeted therapies. Resistance to therapies appears to be a consequence of emergent mutations within the target gene (FGFR2, IDH1), and the development of second-generation multitarget compounds is ongoing.

A primary difficulty for clinicians is the choice of profiling platform. Most commercially available platforms use hybrid DNA technologies, but these are likely to be less good at finding fusion abnormalities. This is currently also the case for liquid biopsies most of which still use DNA technologies and are limited by patient tumour load. A careful discussion of the options with a molecular tumour board is therefore essential.

FGFR2 fusions, mutations and extracellular domain insertions are sensitive to FGF2 inhibitors. Several agents, such as pemigatinib and infigratinib (among others), are likely to have a similar efficacy, affording a progression-free survival in second and subsequent line therapy of 7–9 months. Molecular data from this small number of patients, supported by in vitro data, suggest that futibatinib has shown activity against emergent mutations, but this has yet to be confirmed. Any survival impact is currently uncertain because of the lack of randomised data to resolve the prognostic impact of FGFR2 alterations, which remain uncertain. Short-term toxicities are generally tolerable and manageable, although longer term emergent toxicities, such as hyperphosphataemia, may be more difficult to manage.

Ivosidenib has been shown to have progression-free survival advantage for patients with IDH1 mutations and is now adopted as standard of care in several countries, also after prior treatment with chemotherapy. Similar to FGFR2, resistance emerges through drug-resistant subclones. The primary co-occurring alterations are mutations within P53KCA and may offer rational options for combination therapy as ivosidenib is very well tolerated.

HER2 has been successfully targeted in cholangiocarcinoma, and we await randomised studies to establish optimal sequencing and biomarkers.

Although there has been significant progress, notable challenges remain. Some biliary tract cancers, notably pCCA, are unlikely to be able to receive targeted therapy because of no apparent actionable alterations at present, but additionally the difficulty of obtaining sufficient material for profiling. Additionally, more than 50% of biliary tract cancers do not have an actionable alteration for which targeting pathways, rather than point alterations, might represent a feasible treatment option.

Finally, a number of potentially actionable alterations occur at very low frequency—for instance, BRAFV600E and IDH2 mutations. It is essential, but challenging, to incorporate these patients in clinical studies in order to provide a practice informing outcome. Targeted therapies approved by NICE are shown in Table 6. Potentially beneficial therapies not precluded should be considered in the context of local approval of compassionate use programmes and clinical trials.

### RADIOTHERAPY

**Recommendation 42:** Consider the use of adjuvant chemoradiotherapy for extrarehepatic CCA and gallbladder cancer and a microscopically positive surgical margin resection (R1 resection) with a shared decision-making approach, considering the risk of potential harm and potential for benefit.

*Strength of recommendation: MODERATE
Quality of evidence: MODERATE*

**Recommendation 43:** Consider the delivery of SBRT or PBT in patients with locally advanced inoperable CCA who have received systemic therapy. Modern radiotherapy techniques should be employed to maximise radiotherapy dose and minimise toxicity.

*Strength of recommendation: MODERATE
Quality of evidence: LOW*

**Recommendation 44a:** Refer patients with symptomatic metastatic disease for consideration of palliative radiotherapy.

*Strength of recommendation: MODERATE
Quality of evidence: LOW*

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**Table 6** Frequencies of targeted actionable alterations in biliary tract cancer

<table>
<thead>
<tr>
<th>Alteration</th>
<th>Frequency</th>
<th>Frequency (specific subtype)</th>
<th>Test</th>
<th>ESCAT score</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH1 mutations*</td>
<td>1–18%</td>
<td>8–18% (iCCC)</td>
<td>NGS</td>
<td>IA</td>
<td>113 14</td>
</tr>
<tr>
<td>IDH2 mutations</td>
<td>&lt;5%</td>
<td>&lt;5% (iCCC)</td>
<td>NGS</td>
<td>IIB</td>
<td>114</td>
</tr>
<tr>
<td>FGFR2 fusions+</td>
<td>&lt;10%</td>
<td>5–15% (iCCC)</td>
<td>RNA-seq</td>
<td>IIB</td>
<td>6–9 15–19</td>
</tr>
<tr>
<td>FGFR2 mutations</td>
<td>2%</td>
<td>2% (iCCC)</td>
<td>NGS</td>
<td>IIB</td>
<td>11–15–21</td>
</tr>
<tr>
<td>HER2 amplifications</td>
<td>5–10%</td>
<td>10–20% (dpCCC, GBC)</td>
<td>NGS/FISH/IHC</td>
<td>IIIA</td>
<td>10–15–19 22–24</td>
</tr>
<tr>
<td>HER2 mutations</td>
<td>3–5%</td>
<td>More frequent dpCCC and GBC</td>
<td>NGS</td>
<td>IIIA</td>
<td>10–15–19–22–24</td>
</tr>
<tr>
<td>BRAF mutations</td>
<td>&lt; 5% (50% V600E)</td>
<td></td>
<td>NGS</td>
<td>IIIA</td>
<td>15–19 21 23 25 26</td>
</tr>
<tr>
<td>BRCA1/2 mutations</td>
<td>3–5%</td>
<td></td>
<td>NGS</td>
<td>IIIA</td>
<td>15–19 23 26–32</td>
</tr>
<tr>
<td>PALB2 mutations</td>
<td>1%</td>
<td></td>
<td>NGS</td>
<td>IIIA</td>
<td>1 19 30–33</td>
</tr>
<tr>
<td>KRAS G12C</td>
<td>&lt;1%</td>
<td></td>
<td>NGS</td>
<td>IIIA</td>
<td>1 34</td>
</tr>
<tr>
<td>NTRK</td>
<td>&lt;1%</td>
<td></td>
<td>RNA-seq</td>
<td></td>
<td>1 35</td>
</tr>
<tr>
<td>MSI</td>
<td>&lt;1%</td>
<td></td>
<td>IHC</td>
<td></td>
<td>1 36</td>
</tr>
<tr>
<td>MDM2 amplification</td>
<td>7%</td>
<td></td>
<td>NGS</td>
<td>IIB</td>
<td>37</td>
</tr>
</tbody>
</table>

There is substantial heterogeneity across studies in molecular testing methodology and patient population, which limits the precision of these estimates (approved by the National Institute for Health and Care Excellence at the time of writing).

d/pCCC, distal/perihilar cholangiocarcinoma; FISH, fluorescent in situ hybridisation; GBC, gallbladder cancer; iCCC, intrahepatic cholangiocarcinoma; NGS, next-generation sequencing.
Quality of evidence: MODERATE
Recommendation 44b: Refer for SBRT in the setting of oligometastatic disease.

Strength of recommendation: MODERATE
Quality of evidence: MODERATE

Technological advances, including intensity-modulated/volumetric arc therapy, SBRT, image guidance and the availability of PBT, have enabled the safe and effective use of radiotherapy in the treatment of primary liver cancers. There is growing interest in the use of radiotherapy for the treatment of CCA.

Neoadjuvant

Neoadjuvant radiotherapy is currently used before attempted resection of locally advanced disease or during multimodality therapy prior to liver transplantation. Two systematic reviews on the use of chemoradiotherapy prior to resection of pCCA were of limited quality with variable treatment protocols and limited the reporting of outcomes. Data, however, demonstrate that treatment can be delivered safely in patients with unresectable disease and, in some, facilitates complete resection.

Several retrospective series report outcomes following neoadjuvant radiotherapy/SBRT prior to liver transplantation for pCCA. This approach is now a standard of care in numerous high-volume liver transplant centres worldwide. The largest reported multicentre series included 287 patients with unresectable disease who received neoadjuvant radiotherapy with concurrent and/or maintenance chemotherapy. Intention-to-treat 2- and 5-year overall survival rates were encouraging at 68% and 53%, respectively. One prospective study showed high rates of dropout and disease progression, highlighting the importance of careful patient selection.

A recently published meta-analysis (of mostly retrospective studies) reporting outcomes following transplantation for unresectable pCCA supports a role for neoadjuvant chemoradiotherapy in potentially improving survival outcomes. The ongoing French phase III TRANSPhIL trial (NCT02232932) compares this strategy with standard surgical resection.

Adjuvant

Several meta-analyses have been published on the role of adjuvant radiotherapy. One included 21 retrospective studies of more than 1400 patients with eCCA and gallbladder cancer. The 5-year overall survival rate was higher with adjuvant radiotherapy than in the non-radiotherapy group (OR=0.63, p=0.0002), with particular benefit in patients with lymph node positive disease (OR=0.15, p<0.00001) and positive surgical margins (OR=0.40, p=0.02). Local recurrence rates were reduced in those receiving radiotherapy, but no difference was demonstrated in the rate of distant metastases.

A recent meta-analysis of retrospective studies of a variety of adjuvant therapies for iCCA showed a statistically significant benefit for the use of adjuvant chemoradiotherapy (HR=0.73, 95% CI 0.57 to 0.89), but not radiotherapy alone (HR=0.71, 95% CI 0.39 to 1.03). The use of adjuvant therapy was particularly beneficial in the setting of positive resection margin or lymph node metastases.

A phase II feasibility study of combination adjuvant chemotherapy and chemoradiotherapy in patients with pancreaticobiliary cancers (24% biliary tract cancers) reported tolerability in the adjuvant setting, although 14.5% discontinued study therapy and 15% experienced grade 3+ toxicities with one death. The SWOG S0809 phase II trial enrolled patients with resected eCCA (68%) and gallbladder cancer, who were treated with adjuvant gemcitabine and capecitabine chemotherapy followed by chemoradiotherapy with oral capecitabine. Modern radiotherapy techniques were used, and a comprehensive quality assurance process employed for all cases. The 2-year overall survival rates of 67% and 60%, in R0 and R1 resection patients, respectively, were significantly higher than those expected from historical controls. Acceptable toxicity rates, with 86% patients completing all planned treatment, demonstrate tolerability of the regimen.

Definitive radiotherapy

Definitive chemoradiotherapy and SBRT have been used in the setting of locally advanced inoperable CCA. A systematic review of 11 mixed prospective and retrospective studies of SBRT in unresectable or recurrent CCA demonstrated a 1-year local control rate of 74.7–81.8% depending on radiotherapy dose, with benefit for higher dose. Median overall survival was 13.6 months. Most common toxicity was related to luminal gastrointestinal tissues, with a late incidence of ulceration from 10% to 20%. A further systematic review reported pooled 1-year local control and overall survival rates of 83.4% and 58.3%, respectively. The rate of gastroduodenal complications was variable, with studies including a range of disease location and SBRT dose/fractions.

The phase II Fédération Francophone de Cancérologie Digestive trial randomised patients with CCA and gallbladder cancer to gemcitabine oxaliplatin chemotherapy or radiotherapy delivered concurrently with cisplatin and 5-fluorouracil. No additional chemotherapy was delivered in the chemoradiotherapy arm other than the concurrent dosing. The trial closed early owing to slow accrual, and reported chemotherapy to be at least as effective as chemoradiotherapy.

Hong et al. reported a phase II multi-institutional study investigating the use of PBT in patients with unresectable iCCA and hepatocellular carcinoma. Multifocal disease and tumours with vascular invasion were included. Given the locally advanced nature of these cancers, the 2-year local control rate of 94.1% for the CCA cohort is encouraging, and treatment was delivered with low rates of grade 3+ toxicity.

Dose delivered correlates with outcome for SBRT and conventionally fractionated radiotherapy. Despite 20% having metastatic disease, Tao et al. reported 3-year overall survival and local control rates of 73% and 78%, respectively, for patients with iCCA who received higher radiotherapy doses. Treatment was well tolerated and almost all patients received chemotherapy before radiotherapy/chemoradiotherapy. Brunner et al. reported improved survival and disease control rates with higher SBRT dose for both iCCA and eCCA, with <5% grade 3 toxicity.

A systematic review of the impact of treatment on quality of life shows SBRT to be well tolerated. The addition of SBRT to systemic chemotherapy in locally advanced biliary tract cancers is being investigated in a randomised phase II trial ABC07 (ISRCTN10639756).

Palliative radiotherapy

Palliative radiotherapy can be considered, to manage symptoms such as pain or bleeding caused by metastatic disease. A meta-analysis of retrospective and small single centre randomised controlled trials assessing intraluminal brachytherapy compared with biliary stenting alone in the management of malignant obstructive jaundice reported improvements in risk of stent occlusion and mean survival, with comparable complication...
rate. Availability of expertise in the use of intraluminal brachytherapy limits it use.

Radiotherapy for oligometastatic/recurrence disease
The phase II SABR-COMET trial has shown an improvement in overall survival and no detriment in quality of life with the addition of SBRT to standard of care in patients with 1–5 sites of oligometastatic disease from a variety of primary malignancies. While phase III trial results are awaited to confirm the survival advantage, data from a prospective UK multicentre registry show that SBRT can be delivered safely with encouraging outcomes and has led to commissioning of SBRT by NHS England.

PALLIATIVE CARE
Recommendation 45: All patients with incurable CCA should have access to a palliative care assessment to fully evaluate their holistic care needs. Evidence suggests that early palliative care is associated with higher health-related quality of life and lower rates of depression. Good symptom control should be delivered alongside active oncology management.

Recommendation 46: Development and funding of clinical trials is key to fully evaluate the impact of pharmacological management of symptoms in patients with CCA and different models of care.

PATIENT/PUBLIC PERSPECTIVE
Recommendation 47: All patients diagnosed with CCA should have access to a hepatobiliary cancer nurse specialist who can provide expertise and support to the patient and their immediate family.

Recommendation 48: All patients diagnosed with CCA should have access to a dietician.

Recommendation 49: All patients diagnosed with CCA should have timely access to high-quality information and should be directed to a dedicated CCA patient charity so that they can access support and information.

Recommendation 50: All patients with CCA should be facilitated to access a second specialist clinical opinion if they need to seek reassurance about either their diagnosis or treatment.

The pathophysiology of cholestatic itch is complex and no single treatment has been identified as definitive. It can, however, be a hugely disabling problem for patients with an impact on quality of life. Biliary stenting is an established treatment, with evidence to support the use of metal rather than plastic stents. There is variable evidence available to support the pharmacological management of cholestatic itch. Treatment aims of cholestatic itch are threefold. First, to remove pruritogens from the enterohepatic circulation (eg, cholestyramine or biliary drainage), second to alter the metabolism of pruritogens in the liver and/or gut (eg, rifampicin) and third, to modify central itch signals by influencing specific receptors in the central nervous system (eg, selective serotonin reuptake inhibitors, serotonin receptor antagonists and opioid antagonists). The evidence underpinning all options is limited, although increasing, so for any intervention the severity of the symptom must be clearly defined, and any pharmacological intervention carefully monitored, including benefits and side effects.

The key priority of management of symptoms in patients with CCA includes detailed history taking and identification of symptoms and their severity. Identification of likely aetiology, either disease or treatment related, including specific drug-related toxicities. Pharmacological and non-pharmacological approaches to the management of all symptoms should be considered, alongside appropriate psychosocial support. A multiprofessional approach to management of all patients with CCA, whatever the stage of presentation, is key.

The phase II SABR-COMET trial has shown an improvement in overall survival and no detriment in quality of life with the addition of SBRT to standard of care in patients with 1–5 sites of oligometastatic disease from a variety of primary malignancies. While phase III trial results are awaited to confirm the survival advantage, data from a prospective UK multicentre registry show that SBRT can be delivered safely with encouraging outcomes and has led to commissioning of SBRT by NHS England.
For patients who are potentially operable they should expect to (1) receive clear instructions of the proposed surgery, (2) understand the expected length of stay, (3) the unit’s morbidity and mortality for the proposed operation, (4) the expected date of their surgery, (5) what follow-up they will receive after their operation. Liver transplantation should be considered as a potential management option for qualifying cases, under new guidance.

Patients undergoing preoperative/pretreatment endoscopic procedures or interventional radiological procedures should receive high-quality information about the procedure and the associated risks.

All patients with CCA should have access to a Dietitian/Nutritionist, and this is especially important for resected patients. These patients should be able to contact a dietitian/nutritionist experienced in caring for those who have had this type of surgery, so that they can be advised if they experience symptoms and difficulties with diet and digestion following surgery. Bile acid malabsorption and small intestinal bacterial overgrowth are both relatively common for resected patients with CCA, causing distressing symptoms, and should be considered by healthcare professionals in symptomatic patients.

After potentially curative treatment, given the high recurrence risk, patients should expect regular follow-up. The European Society of Medical Oncology clinical practice guidelines, for example, recommend 3-monthly visits at their specialist centre, and during the first 2 years after surgery patients should expect to receive a clinical examination, laboratory investigation and follow-up CT scans of the thorax, abdomen and pelvis. Regular visits can be extended to 6-monthly thereafter and prolonged to yearly visits after 5 years of follow-up.294

**Systemic therapy, targeted therapy, molecular profiling and clinical trials**

For patients offered systemic therapy, the implications should be fully discussed with their consultant and their clinical nurse specialist. Patients should be given realistic information about the procedure and what it might mean for their quality of life and for their life expectancy, and what side effects might occur. They should know what action to take if they have worrying side effects or symptoms that concern them, and be given contact numbers for advice and help.

With a growing number of clinical studies investigating first-line treatments for those with CCA, any that are available at the time of a patient’s diagnosis should be discussed with the patient before a decision on a first-line treatment is made. Patients should be fully informed about taking part in a clinical trial before making a decision to participate.

Whenever a patient with CCA is deemed inoperable and undergoes a systemic first-line treatment, they should be further assessed by an HPB MDT for operability, either at the mid-way scan or at the end of the first line treatment. They should also have molecular profiling of their tumour.

As described earlier in the guidelines, a significant proportion of CCA have an actionable molecular alteration (table 6). With the advent of treatments targeting certain of these alterations, there are a growing number of clinical trials investigating efficacy. Some trials have reported positively and a number of treatments have now been approved in the USA and in other countries. In 2022, for the first time NICE approved a therapy for those with CCA and an FGFR2 fusion who have previously undergone a first-line therapy. Until this point, molecular profiling was available to the few who were being investigated for eligibility for clinical trials. Importantly, this NICE decision made molecular profiling available to far more patients with CCA.

Stenting is an important area in the management of many patients with CCA. This procedure, what will be involved, why it is needed and what will happen afterwards, should be explained to the patient. Stenting should be carried out only by those endoscopists and interventional radiologists who are experienced in biliary stenting. Following a stenting procedure, patients should be given information on the possibility of biliary infection following a stenting procedure, what action to take if symptoms of cholangitis occur and contact numbers for advice and help.

Symptoms associated with CCA, such as pain, itching or jaundice, will have a detrimental effect on the quality of a patient’s life. All patients should have their symptoms dealt with promptly and appropriately.288 290

**Patient perspectives and support groups**

Patients with CCA are reported to have lower measured physical and psychological health-related quality of life scores than controls as well as anxiety, depression and social isolation. Patients and their loved ones should be encouraged to participate in support groups,292 and be made aware of appropriate support agencies, such as:

► **AMMF**—The Cholangiocarcinoma Charity—is the main UK support group for people with CCA and their loved ones. The AMMF website provides CCA-specific, patient-friendly details, information on new developments and clinical trials, a discussion forum and links to private discussion groups for those with CCA, plus other tools and information important to patients (https://www.ammf.org.uk).

► **Macmillan Cancer Support** can offer general help and advice to those with cancer, especially on where to find benefits and financial support (https://www.macmillan.org.uk/).

► **PSC Support UK** is the only UK patient organisation dedicated to improving the lives of people affected by PSC. They provide patients and families with high-quality, accessible information and support, and collaborate with healthcare providers to improve clinical care (https://www.pscsupport.org.uk).

**CLIMATE CHANGE AND SUSTAINABILITY**

The impact of climate change on CCA is unknown, but fluctuations in carcinogenic toxins excreted via the hepatobiliary system, waterborne infections and parasitic infestations could potentially be affecting disease rates around the world.239 Further data are needed to confirm these inter-relationships.

As with many aspects of healthcare, the care of patients with CCA may contribute to adverse climatic and ecological effects. Given the widespread requirement of ERCP in the management of patients with CCA, we are supportive of the concept of a more sustainable future for endoscopy as has been promoted by the “Green Endoscopy Group”,290 driven by the observation that endoscopy is the third highest source of waste in a typical hospital.

We have recommended that the management of patients with CCA occurs at centres of expertise, but offering local care where possible without compromising the need for specialist input is important to reduce travelling and greenhouse gas emissions. Further examples of good environmental practice that should be considered include reducing unnecessary tests and in-person clinic visits, increased virtual consultations, reduction of waste (for example, in packaging of medications and devices) and...
PRIORITIES FOR SERVICE DEVELOPMENT AND RESEARCH IN CHOLANGIOCARCINOMA
This section summarises the authors’ views on the priorities for service development and research in CCA.

Epidemiology and aetiology
- Monitor future trends with the latest ICD coding system (ICD-11), which includes separate codes for pCCA.
- Investigate possible causes of geographical variation.
- Uncover additional risk factors and drivers for sporadic CCA and focus on developing pan-UK biobanks for CCA research.

Pathology
- Improve the cytological/tissue diagnosis of biliary strictures using ancillary methods—for example, gene sequencing.
- Characterise the tumour microenvironment to improve patient selection for immunotherapy and other systemic treatments, including neoadjuvant therapy. Digital image analysis with multiplex immunohistochemistry and machine learning enables the assessment of immune cell populations, cell–cell interactions and checkpoint marker expression in a time-efficient, quantitative, reproducible manner.
- Elucidate resistance mechanisms to molecular targeted therapy. A second mutation in the target gene, concomitant and acquired mutations in other genes, and activation of other pathways are potential mechanisms of resistance.

Imaging
- Improve detection rates of CCA in PSC and assess benefit of imaging surveillance programmes.
- Determine the most effective method of assessing the function of the future liver remnant to aid surgical planning.

Endoscopy
- Develop and validate next-generation sequencing of bile in the diagnosis of CCA.
- Examine the best drainage option for perihilar CCA undergoing both surgery and palliation.

Surgery
- Optimal preoperative stenting, PTC versus ERCP, has been examined by the DRAINAGE trial, but is there a role for metal stents.
- Neoadjuvant and adjuvant studies, especially the role of targeted therapies in the adjuvant setting.
- Follow-up after resection, role of CT-DNA, long term quality of life metrics.
- Optimum management of oligometastatic disease.
- Establishment of liver transplantation for selected patients with CCA and monitoring of outcomes.

Systemic treatment
- Access to molecular profiling.
- Widen access to clinical trials.

Radiotherapy
- Optimum patient selection for photon or particle radiotherapy.

Identify molecular signatures/biomarkers in order to develop optimal combinations and sequencing of radiotherapy and biological agents (eg, DNA damage response pathway, immune signature).
- Identify a ‘low-metastatic potential’ tumour phenotype that would benefit from the use of ablative local/radiotherapy treatments.

Palliative care
- Develop evidence to confirm the benefit of early palliative care intervention in patients with CCA.
- Increase evidence to inform the best models of care for integration between oncology and palliative care services.
- Increase the evidence underpinning the use of various pharmacological interventions to treat specific symptoms.

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Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplementary Figure 1: Intrahepatic CCA staging is conducted most commonly in accordance with the TNM staging classification of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC). As of 2018, the staging criteria are in their 8th edition and reflected below

Primary tumour (T)
TX: primary tumour cannot be assessed
T0: no evidence of primary tumour
Tis: carcinoma in situ (intraductal tumour)
T1: solitary tumour without vascular invasion
T1a: solitary tumour ≤5 cm without vascular invasion
T1b: solitary tumour >5 cm without vascular invasion
T2: solitary tumour with intrahepatic vascular invasion or, multiple tumours, with or without vascular invasion
T3: tumour perforating the visceral peritoneum
T4: tumour involving local extrahepatic structures by direct invasion

Regional lymph node (N)
NX: regional lymph nodes cannot be assessed
N0: no regional lymph node metastasis
N1: regional lymph node metastasis present

Distant metastases (M)
cM0: no evidence of metastases
cM1: distant metastasis
pM1: distant metastasis, microscopically confirmed

Stage groups
stage 0
Tis, N0, M0
stage IA
T1a, N0, M0
stage IB
T1b, N0, M0  
stage II  
T2, N0, M0  
stage IIIA  
T3, N0, M0  
stage IIIB  
T4, N0, M0  
[Any T], N1, M0  
stage IV  
[Any T], [Any N], M1

Prognosis

The 5-year survival for each stage of iCCA in the AJCC 8th edition is as follows:

- stage IA: 58%
- stage IB: 45%
- stage II: 31%
- stage IIIA: 24%
- stage IIIB: 12%
- stage IV: 9%
Supplementary Figure 2: Perihilar CCA staging is, for prognostication, most commonly conducted using the TNM staging classification of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC).

Primary tumour (T)
TX: primary tumour cannot be assessed
T0: no evidence of primary tumour
Tis: carcinoma in situ/high-grade dysplasia
T1: tumour confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2:
T2a: tumour invades beyond the wall of the bile duct to surrounding adipose tissue
T2b: tumour invades adjacent hepatic parenchyma
T3: tumour invades unilateral branches of the portal vein or hepatic artery
T4:
tumour invades the main portal vein or its branches bilaterally, or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
Regional lymph node (N)
The regional lymph nodes are hilar, cystic duct, common bile duct, hepatic artery, posterior pancreaticoduodenal, and portal vein lymph nodes.

NX: regional lymph nodes cannot be assessed
N0: no regional lymph node metastasis
N1: 1-3 positive regional lymph nodes
N2: 4 or more positive regional lymph nodes
Distant metastases (M)
cM0: no evidence of metastases
cM1: distant metastasis
pM1: distant metastasis, microscopically confirmed
Stage groups
stage 0
Tis, N0, M0
stage I
T1, N0, M0
stage II
[T2a, T2b], N0, M0
stage IIIA
T3, N0, M0
stage IIIB
T4, N0, M0
stage IIIC
[Any T], N1, M0
stage IVA
[Any T], N2, M0
stage IVB
[Any T], [Any N], M1
Supplementary Figure 3: Distal CCA staging is defined according to the TNM staging classification of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC). As of 2018, the staging criteria are in their 8th edition and reflected below

**Primary tumour (T)**
- TX: primary tumour cannot be assessed
- Tis: carcinoma in situ/high-grade dysplasia
- T1: tumour invades the bile duct wall with depth <5 mm
- T2: tumour invades the bile duct wall with depth 5–12 mm
- T3: tumour invades the bile duct wall with depth >12 mm
- T4: tumour involves the coeliac axis, superior mesenteric artery, and/or common hepatic artery

**Regional lymph node (N)**
- NX: regional lymph nodes cannot be assessed
- N0: no regional lymph node metastasis
- N1: 1–3 positive regional lymph nodes
- N2: 4 or more positive regional lymph nodes

**Distant metastases (M)**
- cM0: no evidence of metastases
- cM1: distant metastasis
- pM1: distant metastasis, microscopically confirmed

**Stage groups**
- stage 0
  - Tis, N0, M0
- stage I
  - T1, N0, M0
- stage IIA
  - T1, N1, M0
  - T2, N0, M0
- stage IIIB
  - T2, N1, M0
  - T3, [N0, N1], M0
- stage IIIA
  - [T1, T2, T3], N2, M0
- stage IIIB
T4, [N0, N1, N2], M0
stage IV
[Any T], [Any N], M1