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## **National guidelines for the diagnosis and treatment of hilar cholangiocarcinoma**

Dar FS *et al.* National guidelines for hilar CCA

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### **Abstract**

A consensus meeting of national experts from all major national hepatobiliary centres in the country was held on May 26, 2023, at the Pakistan Kidney and Liver Institute & Research Centre (PKLI & RC) after initial consultations with the experts. The Pakistan Society of Study of Liver Diseases (PSSLD) and PKLI & RC jointly organised this meeting. This effort was based on a comprehensive literature review to establish national practice guidelines for hilar cholangiocarcinoma (hCCA). The consensus was that hCCA is a complex disease and requires a multidisciplinary team approach to best manage these patients. This coordinated effort can minimise delays and give patients a chance for curative treatment and effective palliation. The diagnostic and staging workup includes high-quality computed tomography, magnetic resonance imaging, and magnetic resonance cholangiopancreatography. Brush cytology or biopsy utilizing endoscopic retrograde cholangiopancreatography is a mainstay for diagnosis. However, histopathologic confirmation is not always required before resection. Endoscopic ultrasound with fine needle aspiration of regional lymph nodes and positron emission tomography scan are valuable adjuncts for staging. The only curative treatment is the

surgical resection of the biliary tree based on the Bismuth-Corlette classification. Selected patients with unresectable hCCA can be considered for liver transplantation. Adjuvant chemotherapy should be offered to patients with a high risk of recurrence. The use of preoperative biliary drainage and the need for portal vein embolization should be based on local multidisciplinary discussions. Patients with acute cholangitis can be drained with endoscopic or percutaneous biliary drainage. Palliative chemotherapy with cisplatin and gemcitabine has shown improved survival in patients with irresectable and recurrent hCCA.

**Key Words:** Hilar cholangiocarcinoma; Bismuth-Corlette classification; Memorial Sloan Kettering Cancer Centre Staging; Preoperative biliary drainage; Portal vein embolization; Surgical resection; Hepatectomy

Dar FS, Abbas Z, Ahmed I, Atique M, Aujla UI, Azeemuddin M, Aziz Z, Bhatti ABH, Bangash TA, Butt AS, Butt OT, Dogar AW, Farooqi JL, Hanif F, Haider J, Haider S, Hassan SM, Jabbar A, Khan AN, Khan MS, Khan MY, Latif A, Luck NH, Malik AK, Rashid K, Rashid S, Salih M, Saeed A, Salamat A, Tayyab GUN, Yusuf A, Zia HH, Naveed A. National guidelines for the diagnosis and treatment of hilar cholangiocarcinoma. *World J Gastroenterol* 2024; In press

**Core Tip:** Consensus among national hepatobiliary experts convened at the Pakistan Kidney and Liver Institute & Research Centre emphasized the complexity of hilar cholangiocarcinoma (hCCA), advocating a multidisciplinary approach for optimal patient management. Diagnostic protocol includes imaging like computed tomography, magnetic resonance imaging, and magnetic resonance cholangiopancreatography, while endoscopic retrograde cholangiopancreatography plays an important role in tissue acquisition. Surgical resection remains the best curative treatment option. For unresectable cases, liver transplantation is considered under strict selection criteria. Preoperative biliary drainage and portal vein embolization decisions may be needed for

selective cases. Adjuvant chemotherapy addresses the risk of recurrence. The role of Immunotherapy is emerging and offers improved survival for irresectable hCCA.

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## **INTRODUCTION**

Cholangiocarcinoma (CCA) is the second most common liver-related cancer. It accounts for 10%-20% of mortalities from hepatobiliary malignancies. Hilar CCA (hCCA) is the most frequent type, accounting for 40%-60% of cases. There is currently no national consensus in Pakistan for the appropriate diagnosis and treatment of hCCA. To address this gap, the Pakistan Society of Study of Liver Diseases (PSSLD) and the Pakistan Kidney and Liver Institute & Research Centre (PKLI & RC) collaborated to conduct a consensus meeting to develop guidelines. These guidelines aim to standardise diagnostic approaches and treatment strategies for patients nationwide.

## **DEVELOPMENT OF GUIDELINES**

With no comprehensive national registry and the scarcity of formal hepatobiliary centres, diagnosis, and treatment of hCCA remained suboptimal for patients in Pakistan. However, more recently, with the development of hepatobiliary centres in major cities, there was a need for national consensus to develop appropriate patient pathways for the diagnosis and treatment of hCCA. The need for such national guidelines was realized and discussions with experts were initiated. Following initial consultations with the collaborative efforts of the PSSLD and the PKLI & RC, a consensus meeting of national experts from all major hepatobiliary centres was arranged on May 26, 2023, at PKLI & RC, Lahore, Pakistan.

## **INTENT**

These guidelines are developed to standardize patients' diagnostic approaches and treatment strategies nationwide. The basis of guidelines is the literature review of randomised controlled trials (RCT), meta-analyses, case cohorts and prospective and retrospective studies. These guidelines should not be regarded as the standard of care



for all patients. Patients must be managed based on all available clinical data for that case. The guidelines are subject to change, considering future advances in scientific knowledge.

## **LEVEL OF EVIDENCE**

The recommendations are graded according to the Oxford Centre for Evidence-Based Medicine, adapted from the Oxford 2011 Levels of Evidence (Table 1).

## **EPIDEMIOLOGY**

CCA is the second most common liver-related cancer<sup>[1]</sup>. It accounts for 10%-20% of mortalities from hepatobiliary malignancies<sup>[1]</sup>. Anatomically, it is classified as intrahepatic and extrahepatic. Extrahepatic CCA (eCCA) is then further classified as hilar/perihilar (hCCA) and distal (dCCA) based on location. Intrahepatic CCA (iCCA) occurs above the second-order bile ducts, while the insertion of the cystic duct distinguishes the hCCA and dCCA types<sup>[2]</sup> (Figure 1).

HCCA, or Klatskin tumour, is the most common type, accounting for 40%-60% of CCA cases, followed by dCCA at 20%-30% and iCCA at 10%-20%<sup>[3]</sup>. Variances in etiology, risk factors, pathobiology, clinical management, and prognosis are based on these anatomical differences. Until 2022, the International Classification of Diseases (ICD) did not have a specific code for CCA, resulting in misclassification and difficulty in identifying disease characteristics. The ICD-11 codes were published on January 1, 2022 and now include separate codes for each subtype of CCA<sup>[4]</sup> (Figure 1). The introduction of these new codes will help differentiate the three subtypes of CCA.

CCA typically occurs in individuals over 40, most commonly in the seventh decade of life<sup>[5]</sup>. Men are more likely to develop CCA than women, with a ratio of 1.0:1.2-1.5<sup>[6]</sup>. Incidence has been on the rise globally in recent decades, with an increase in mortality for iCCA<sup>[7]</sup>. It has a significant geographical variation and is less common in Western countries compared to some parts of Asia. This difference is mainly attributed to the

higher prevalence of established risk factors in some Asian countries. Incidence per 100000 ranges from 85 in northeast Thailand to 0.4 in Canada<sup>[8]</sup>.

Epidemiological data on hCCA is lacking from Pakistan. Only a few local retrospective studies are available on outcomes. Recently, a National Cancer Registry report from Pakistan (2015-2019) showed that liver and intrahepatic bile duct cancers represent 4.43% of all cancers, with a higher prevalence in men compared to women (6.73 vs 2.45)<sup>[9]</sup>. In a retrospective analysis of 245 patients with biliary tract malignancy at Aga Khan University, 11.8% were diagnosed with CCA<sup>[10]</sup>. In another report from Lahore, 34 patients were operated on for CCA over nine years, hCCA represented 53% of these cases<sup>[11]</sup>. Dar *et al*<sup>[12]</sup> in their analysis of 24 patients with hCCA, reported a median age at presentation of 49 (23-73) years, with male to female ratio of 1.4:1.0.

### **Risk factors**

The causes of hCCA remain obscure in many patients. The role of genetic factors needs to be better defined<sup>[13,14]</sup>. The estimated lifetime incidence of CCA with primary sclerosing cholangitis (PSC) ranges up to 20%<sup>[15]</sup>. While PSC is a known risk factor for CCA<sup>[16]</sup>, it is attributed to no more than 10% of CCA cases<sup>[17]</sup>. Hepatobiliary flukes, specifically *Opisthorchis viverrini* and *Clonorchis sinensis* have been linked to the development of CCA in Southeast Asia, regardless of site<sup>[18]</sup>. The presence of hepatitis B virus (HBV) and hepatitis C virus (HCV) has been linked to an increased risk of developing iCC<sup>[3]</sup>. Studies do not confirm the association of HBV or HCV with hCCA. Cirrhosis is consistently identified as a risk factor for iCC but not for hCCA<sup>[19]</sup>. In a meta-analysis by Clements *et al*<sup>[19]</sup> choledocholithiasis showed a stronger association with eCCA than iCCA, with odds ratios of 18.58 and 10.08, respectively. Choledochal cysts conferred the most significant risk of both iCCA and eCCA with pooled odds ratio of 26.71 [95% confidence interval (95%CI): 15.80-45.16] and 34.94 (95%CI: 24.36-50.12), respectively<sup>[19]</sup>.

Available cohort and case-control studies indicate that high levels of alcohol consumption and tobacco smoking can also increase the likelihood of developing CCA,

including hCCA<sup>[20]</sup>. Conditions such as diabetes, obesity, non-alcoholic fatty liver disease and metabolic syndrome are believed to contribute to the increasing incidence of CCA<sup>[3]</sup>. However, no significant associations were found between hypertension and obesity<sup>[19]</sup>. Diabetes has been identified as an important risk factor for both iCCA and eCCA, with odds ratios of 1.8 (95%CI: 1.5-2.1) and 1.5 (95%CI: 1.3-1.8), respectively<sup>[21]</sup> (Table 3).

Association with other risk factors like IgG4-associated sclerosing cholangitis<sup>[22,23]</sup>, abnormal junction between the bile and pancreatic duct<sup>[24]</sup>, typhoid infection<sup>[25,26]</sup>, and infection with *Helicobacter bilis*<sup>[27,28]</sup> need more research before a definitive conclusion can be made.

### ***Recommendations***

**Recommendation 1:** Choledochal cysts, primary sclerosing cholangitis, parasitic infestations, hepatolithiasis and choledocholithiasis should be considered as well-established risk factors for hCCA (LoE 2; strong recommendation).

**Recommendation 2:** Diabetes, alcohol, smoking and obesity should be considered as less well-established risk factors for hCCA (LoE 3; strong recommendation).

## **HISTO-MORPHOLOGICAL CLASSIFICATION**

The CCA can be classified based on anatomy, morphology, and histopathology. Anatomical classification has been discussed earlier in the above section.

### ***Morphology***

They were initially classified as nodular, massive, and diffuse. Rosai called them polypoidal and sclerosing<sup>[29]</sup>. However, at present, the classification from the Japanese group<sup>[30]</sup> is being followed as below: (1) Mass forming is defined as a small nodule 1-2 cm with bile duct dilatation; (2) intraductal (polypoidal, sessile, or superficially spreading) is along the mucosa. It is confined to the mucosa and does not infiltrate

deeply till an advanced stage; and (3) periductal is characterised by annular thickening without mass formation and manifests as complete luminal obstruction.

### *Histology*

Most are classified as well to moderately differentiated biliary-type adenocarcinomas<sup>[31]</sup>. Tubules and glands characterise a typical desmoplastic stroma with a variable inflammatory response. These are further categorised as gastric foveolar, intestinal, and biliary types. Sometimes, papillary groups and sheets are also seen<sup>[32]</sup>. Perineural and neural invasion is a specific route of invasion, seen in many cases and has prognostic significance. There is also increased invasion of lymphatics<sup>[33]</sup>. A quantitative grading system based on the percentage of gland formation has been proposed in College of American Pathologists guidelines and should be followed to standardise reporting<sup>[34]</sup>.

In addition to conventional adenocarcinoma, there are other types, *i.e.*, squamous cell carcinoma, adenosquamous carcinoma, mucinous, signet ring cells, neuroendocrine, clear cells and poorly differentiated. Most of these non-conventional carcinomas have a worse prognosis. Two premalignant conditions have also been identified. High-grade <sup>1</sup> biliary intraepithelial neoplasm and intraductal papillary neoplasm of the biliary tract<sup>[35]</sup>.

Immunohistochemistry can help differentiate metastatic disease by identifying the biliary nature of cells. Conventional markers for adenocarcinomas are CK7, CK20, CK19, P53, MUC5AC, and MUC1. The markers used for squamous cell carcinoma are CK5/6 and for neuroendocrine carcinoma are synaptophysin/chromogranin<sup>[36]</sup>. <sup>24</sup> Lack of mucin production and the expression of HepPar-1, CD10, and glypican-3 helps distinguish hepatocellular carcinoma from CCA.

Immunohistochemistry is helpful in the following two scenarios: To differentiate metastatic disease from primary CCA and to distinguish CCA from hepatocellular cancer<sup>[37]</sup>.

### *Biliary cytology*

It is reported under six categories: (1) Unsatisfactory; (2) <sup>29</sup>negative for malignancy; (3) atypical; (4) benign neoplastic lesions; (5) suspicious for malignancy; and (6) malignant.

### *Molecular pathology*

Gene sequencing to assess molecular alterations is now emerging to differentiate between benign and malignant strictures<sup>[38]</sup>. Singhi *et al*<sup>[39]</sup> evaluated a 28-gene next-generation sequencing panel using biliary specimens from Endoscopic retrograde cholangiopancreatography (ERCP). Next-generation gene sequencing improved sensitivity from 35% to 77% for biliary brushings and 52% to 83% for biliary biopsies.

### *Recommendations*

**Recommendation 3:** hCCA should be classified as conventional adenocarcinomas or other unconventional tumours based on biliary cytology or biopsy (LoE 2; strong recommendation).

**Recommendation 4:** College of American Pathologists guidelines should be followed to standardise reporting (LoE 3; strong recommendation).

**Recommendation 5:** Immunohistochemistry may be done in selected cases to aid diagnosis (LoE 3; weak recommendation).

### **LABORATORY EVALUATION**

Patients generally present with painless jaundice. The alanine aminotransferase/aspartate aminotransferase may be normal or minimally elevated. <sup>27</sup>Alkaline phosphatase levels usually rise in conjunction with bilirubin levels. <sup>27</sup>Biochemical tests of liver function [*i.e.*, albumin, prothrombin time (PT)] are normal early in the course of disease. The PT/INR may be elevated with prolonged obstruction because of vitamin K malabsorption.



None of the tumour markers are highly sensitive or specific for diagnosis. Carbohydrate antigen 19-9 (CA19-9) is the commonly used tumour marker. The CA19-9 is mainly synthesised by the pancreatic and biliary ductal cells and can be falsely raised in biliary and pancreatic ductal obstruction from benign diseases<sup>[40]</sup>. Notably, 10% of the patients are non-producers and may have normal CA19-9 levels<sup>[41]</sup>. The CA19-9 can also be produced by epithelial cells in the stomach, colon, uterus, and salivary glands. Elevated levels can also be seen in urological, pulmonary and gynecological conditions<sup>[42]</sup>.

In patients with PSC, a cut-off value of 129 U/mL had a sensitivity (78.6%), specificity (98.5%), pulse pressure variation (56.6%), and NPV (99.4%) in predicting CCA<sup>[43]</sup>. Another study reported a cut-off value of 100 U/mL having a sensitivity (53.0%) and NPV (92%) in predicting CCA<sup>[41]</sup>. In a meta-analysis published in 2015, the overall pooled sensitivity was 0.72 (0.70-0.75) and specificity was 0.84 (0.82-0.85)<sup>[44]</sup>. The utilization of other tumour markers, *i.e.*, carcinoembryonic antigen (CEA) and CA-125, in diagnosing hCCA is limited due to their low specificity. It cannot be interpreted in the setting of obstruction.

The IgG4 cholangiopathy commonly affects older adults and poses a challenge to diagnosing hCCA, with several reports in the literature<sup>[45-48]</sup>. With greater recognition of this entity, several guidelines<sup>[49-51]</sup> now recommend testing for IgG4 cholangiopathy in those with suspected hCCA.

### **Recommendations**

**Recommendation 6:** CA19-9 is a widely used serum tumour marker for suspected hCCA but does not exhibit high sensitivity and should be carefully interpreted as part of the clinical evaluation (LoE 2; strong recommendation).

**Recommendation 7:** Testing for IgG4 cholangiopathy should be obtained in suspected cases of hCCA (LoE 4; strong recommendation).

## **IMAGING WORKUP**

Ultrasound (US) is generally the first imaging modality to evaluate obstructive jaundice. It cannot directly diagnose hCCA but may raise suspicion. Once the diagnosis of hCCA is suspected, the initial radiological examination is often a <sup>6</sup> cross-sectional imaging study, such as computed tomography (CT) or magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP)<sup>[52,53]</sup>.

The CT is readily available, quick to perform and does not require breath holding, but it carries a risk of radiation exposure and contrast-induced nephropathy. The MRI with MRCP, on the other hand, has no radiation risk; however, it is a longer procedure, needs patient cooperation and may be contraindicated in those with pacemakers and metal implants. While MRI with MRCP is better for soft tissue characterisation and may provide an accurate assessment of longitudinal extension in hCCA, it may overestimate vascular invasion, especially after stenting. The CT, on the other hand, provides better information on vascular invasion<sup>[52]</sup>.

There is no head-to-head comparison of CT *vs* MRI/MRCP in diagnosing hCCA. In a systematic review article by Zhang *et al*<sup>[54]</sup> CT was the most commonly used modality. However, MRI with MRCP is becoming the preferred modality for diagnosing hCCA in the literature<sup>[55]</sup>. In the Pakistani setting, given the limitations of availability, cost and difficulty in acquiring good-quality images, a CT scan can be used as the preferred diagnostic modality<sup>[56]</sup>.

Positron emission tomography (PET)-CT has no clear diagnostic role in helping evaluate issues of local resectability. However, it appears to add some benefit in detecting distant metastatic disease<sup>[57]</sup>. In one study by Kim *et al*<sup>[58]</sup> <sup>11</sup> PET-CT revealed higher accuracy than CT and MRI in the diagnosis of regional lymph node metastases (75.9% *vs* 60.9%,  $P = 0.004$ ) and distant metastases (88.3% *vs* 78.7%,  $P = 0.004$ ). <sup>11</sup> More studies on the application of PET-CT are needed to determine its utility in staging<sup>[54]</sup>. Endoscopic US (EUS) with or without fine needle aspiration (FNA)/fine needle biopsy may offer another alternative in staging metastatic lymph nodes<sup>[59]</sup>.

The necessity of establishing a tissue diagnosis before surgery depends upon the clinical situation<sup>[60]</sup>. It is not critical for planning surgery in patients with characteristic findings of mass-forming malignant biliary obstruction and may not be necessary for planning palliative therapy. Furthermore, tissue sampling with a percutaneous approach with US or CT guidance is not advisable without a visible mass<sup>[61]</sup>. Detailed knowledge of mimicking diseases and interpretation of biochemical and imaging modalities may lead to a correct diagnosis without the need of a biopsy<sup>[61]</sup>.

Given the complexity of diagnosis and staging, each case of suspected hCCA should be discussed in a multidisciplinary team (MDT) meeting. The MDT should comprise of radiologists, advanced gastrointestinal endoscopists, hepatobiliary surgeons and oncologists to decide the need for further testing.

### *Recommendations*

**Recommendation 8:** The initial radiological examination should be a cross-sectional imaging study, such as a CT, MRI, or MRCP (LoE 2; strong recommendation).

**Recommendation 9:** Treatment planning should be done in the presence of resectable hCCA with characteristic imaging features, tissue diagnosis is not mandatory for such cases (LoE 4; weak recommendation).

**Recommendation 10:** PET-CT may aid in diagnosing distant metastatic disease and should be considered in surgical planning, where added information may change the treatment outcome (LoE 2; weak recommendation).

### **ROLE OF ENDOBILIARY PROCEDURES IN DIAGNOSTIC EVALUATION**

The primary purpose of endobiliary interventions in the diagnostic evaluation of hCCA is to establish histological confirmation and disease staging in the context of Bismuth-Corlette classification (Figure 2) to determine resectability and offer preoperative planning. Biliary strictures remain indeterminate without confirmatory histology,



posing a diagnostic dilemma to stratify management decisions. Although in patients with hCCA, preoperative histological confirmation may not be required, around 20% with benign biliary strictures may undergo major surgery for suspected biliary malignancy<sup>[62]</sup>.

The most commonly used modalities for tissue diagnosis in resectable hCCA are ERCP, PTC and intraductal cholangioscopy. Brush cytology, fluoroscopy and cholangioscopy guided forceps biopsy are used to ascertain tissue diagnosis.

The sensitivity of standard brush cytology in the review of 1556 cases has been reported at 41.6%  $\pm$  3.2% (99%CI) with a negative predictive value of 58.0%  $\pm$  3.2% (99%CI)<sup>[63]</sup>. Yoon *et al*<sup>[64]</sup> in a meta-analysis revealed pool diagnostic sensitivity of 56.0% (95%CI: 48.8%-63.1%,  $I^2$  = 83.0%) with brush cytology alone, 67.0% (95%CI: 60.2%-73.5%,  $I^2$  = 72.5%) with biopsy and 70.7% (95%CI: 64.1%-76.8%,  $I^2$  = 42.7%) with brushing & biopsy. Supplementary techniques such as fluorescence in situ hybridization (FISH) have been suggested to improve diagnostic sensitivity further. Nanda *et al*<sup>[65]</sup> reported the diagnostic sensitivity of brush cytology alone, brush cytology with FISH, brush with FISH and biopsy to be 27% vs 77% vs 82%, respectively.

The number of passes also increases the diagnostic sensitivity of brush cytology. Wang *et al*<sup>[66]</sup> in a RCT, showed that the sensitivity of brush cytology was 38%, 47%, and 57% in the 10-times, 20-times, and 30-times groups, respectively ( $P$  = 0.001). The stricture length of > 1 cm has also been reported as a predictive factor of positive diagnostic yield on brush cytology<sup>[67]</sup>.

Single-operator digital cholangioscopy has emerged as a preferred modality for evaluating indeterminate hilar strictures after inconclusive endobiliary investigations. A systematic review evaluated outcomes of cholangioscopy directed biopsies involving 539 patients and reported a pooled sensitivity of 72% and specificity of 99%<sup>[68]</sup>. Sun *et al*<sup>[69]</sup> in a meta-analysis, studied the performance of single-operator cholangioscopy and revealed the pooled sensitivity and specificity of visual impression (90% & 87%) and spy-bite biopsy (69% & 98%) for the diagnosis of indeterminate biliary strictures.

The role of EUS in hCCA is to stage the disease and sample the hilar mass or locoregional lymph nodes. However, tissue acquisition of hilar mass by EUS carries the risk of seeding metastasis and should be decided in MDT settings<sup>[70]</sup>. In a meta-analysis, <sup>38</sup> the pooled diagnostic sensitivity and specificity of EUS FNA for malignant hilar strictures was 76% (95%CI: 66%-85%) and 100% (95%CI: 95%-100%), respectively, with low adverse event rates<sup>[71]</sup>.

Lymph node metastasis is a strong predictor of poor survival in hCCA patients. Malikowski *et al*<sup>[72]</sup> reported better regional lymph node detection rates with EUS (89%) than cross-sectional imaging (48%) in patients with hCCA and malignancy was confirmed in 16% of nodes after tissue acquisition *via* EUS-FNA. Another retrospective, multicentre cohort study demonstrated that EUS-FNA detected malignant lymph nodes in 14% of potentially resectable hCCA and avoided surgical exploration<sup>[73]</sup>.

The role of intraductal US (IDUS) in the evaluation of indeterminate biliary strictures is evolving. In a study of 234 indeterminate biliary strictures, <sup>19</sup> the detection rate of malignancy by ERCP/IDUS was superior to endoscopic trans-papillary biopsy (91% <sup>19</sup> vs 59%,  $P < 0.0001$ ), EUS (91% vs 74%,  $P < 0.0001$ ), and CT (91% vs 73%,  $P < 0.0001$ )<sup>[74]</sup>.

### **Recommendations**

**Recommendation 11:** ERCP guided brush cytology and targeted biopsy should be the preferred diagnostic modality to obtain histological confirmation in suspicious or indeterminate biliary strictures (LoE 2; strong recommendation).

**Recommendation 12:** The number of passes should be increased to enhance the diagnostic sensitivity of brush cytology (LoE 2; strong recommendation).

**Recommendation 13:** Intraductal cholangioscopy and tissue sampling should be considered in selective cases that remain a diagnostic challenge (LoE 2; strong recommendation).

**Recommendation 14:** In cases with concern for locoregional metastasis, EUS should be used for staging and tissue sampling (LoE 4; strong recommendation).

## **STAGING**

Various staging systems have been introduced to define tumour resectability and guide therapy. In 1975 Bismuth and Corlette<sup>[75]</sup> presented the first staging system. Their classification focused primarily on the level and extension of the tumour along the biliary ductal system. This classification correlated to the procedure required for surgical excision and the establishment of biliary continuity<sup>[75,76]</sup>.

To define resectability, the Memorial Sloan Kettering Cancer Centre staging was introduced in 1998 and was revised in 2001. They incorporated the portal vein invasion, the resulting hepatic lobar atrophy, tumour location and extension of bile duct involvement<sup>[77]</sup>. This staging system provides a framework for defining resectability. However, it does not evaluate the presence of nodal/distant metastasis or arterial involvement.

Mayo Clinic staging was designed for outcome prediction of hCCA patients rather than surgical resection. The Mayo Clinic staging considered the tumour size and multifocality, vascular invasion, lymph node, extra-regional metastasis, and CA19-9 level and performance status to categorize patients into a four-stage system. This staging system reported survival for unresectable hCCA<sup>[78,79]</sup>.

The American Joint Commission on Cancer (AJCC) staging system, which includes a tumour-node-metastasis (TNM) system, is based on pathological findings and is known as pathological staging. It is used postoperatively, has a better prognostic value for resected patients and guides further therapy. The AJCC 8<sup>th</sup> edition is currently available<sup>[80]</sup>.

To produce a simple and reproducible staging system for hCCA, the International CCA Working Group recently proposed a new classification based on some parameters from the previous systems<sup>[2]</sup>. The size of the tumour, the extent of the biliary system involvement, hepatic artery and portal vein involvement, lymph node involvement,

distant metastases and the volume of the remnant liver after resection. This system aims to standardise the reporting of hCCA so that resectability and prognosis can be adequately provided.

These staging systems can be supplemented with each other to define resectability, guide the therapy and predict the prognosis in hCCA patients.

### *Recommendations*

**Recommendation 15:** Bismuth-Corlette classification provides the basis for determining the biliary extent of hCCA and should be used for primary staging and deciding on the surgical technique (LoE 1; strong recommendation).

**Recommendation 16:** Memorial Sloan Kettering Cancer Centre staging evaluates blood vessel invasion and liver atrophy and should be used for predicting resectability (LoE 3; strong recommendation).

**Recommendation 17:** American Joint Committee on Cancer TNM staging is based on a comprehensive analysis of postoperative pathological findings. It should be used in predicting the prognosis and postoperative survival of patients (LoE 2; strong recommendation).

### **ASSESSMENT OF RESECTABILITY**

The cardinal principle defining resectability is the presence of adequate functional hepatic parenchyma with the achievement of a negative resection margin along with the ability to restore biliary flow in the absence of distant disease<sup>[60,81]</sup>. Assessment of resectability should be done before any biliary intervention unless the patient is septic. Each case should be discussed in MDT and all hCCA cases should be referred to be managed at high-volume specialist hepatobiliary centres<sup>[82,83]</sup>.

Each patient's clinical condition and performance status are assessed to ensure they can undergo major hepatic surgery<sup>[81]</sup>. Cross-sectional images are discussed in MDT

meetings<sup>[84]</sup> for the extent of biliary involvement, the possibility of R0 resection, anatomical variations in hilar structures, quality of hepatic parenchyma and volume of the intended future liver remnant (FLR)<sup>[81]</sup>. An adequate remnant liver is generally considered as 25% in normal parenchyma<sup>[85]</sup>, while in steatotic and cholestatic livers, the safe limit is 30%-40%<sup>[60,81,85]</sup>. An inadequate remnant liver may necessitate FLR modulation<sup>[12,60,81,86]</sup>.

Irresectability is defined based on the following parameters: (1) Metastatic spread: Once the disease has spread to distant organs, peritoneum and distant lymph nodes<sup>[60,81]</sup>; (2) patient factors: When the patient is not fit to undergo major liver surgery due to comorbid medical conditions or has a cirrhotic liver with portal hypertension<sup>[60,81]</sup>; and (3) local factors: There is no consensus regarding local factors determining irresectability<sup>[86]</sup>, hence requiring consideration of individual patient characteristics in MDT discussion<sup>[84]</sup>.

However, the following criteria make the disease unresectable<sup>[60,81]</sup>: (1) **Bilateral hepatic duct involvement up to secondary biliary radicals**; (2) **encasement/occlusion of the main portal vein**; (3) **encasement of portal vein branch with atrophy of contralateral hepatic lobe**; and (4) **hepatic duct involvement up to secondary biliary radicals with atrophy of the contralateral hepatic lobe**.

Several reports<sup>[12,81,86-88]</sup> recently have shown improved survival in patients with locally advanced disease undergoing major hepatectomies, with portal venous or arterial resection and extended liver resections as right and left trisectionectomies. However, such resections should be performed in highly selected individuals<sup>[60]</sup>. Portal vein resection is associated with a survival advantage<sup>[86,88]</sup>. While the clinical benefits of arterial resection for patients with arterial invasion are still unclear<sup>[86]</sup>, this technique results in a higher rate of R0 resection<sup>[89]</sup>.

### ***Recommendations***



Recommendation 18: The assessment of disease resectability should be done as a part of hepatobiliary MDT meetings, looking at biliary involvement, lobar atrophy, vascular involvement and FLR (LoE2; strong recommendation).

### **PORTAL VEIN EMBOLIZATION**

Most studies have reported that portal vein embolization (PVE) induces significant hypertrophy of the FLR, thereby increasing the chance of curative resection<sup>[90]</sup>. The magnitude of FLR hypertrophy varies depending on the extent of liver disease and the technique of PVE<sup>[91]</sup>. While PVE is generally considered safe, there is a risk of liver failure and other complications, especially in patients with poor liver function or extensive disease. A meta-analysis including 37 publications and 1140 patients undergoing PVE showed liver hypertrophy by an average of 8%-27%, with a complication rate of around 3% and zero mortality<sup>[92,93]</sup>. Some studies have suggested that PVE may be associated with an increased risk of tumour progression or recurrence<sup>[94]</sup>. Still, the evidence is conflicting and the exact mechanisms of this effect still need to be fully understood.

The PVE should only be considered in patients who can achieve resectability with liver hypertrophy<sup>[95]</sup>. The PVE should be performed early enough to allow for adequate FLR hypertrophy but not too early to allow tumour progression<sup>[95]</sup>.

Segment-IV branch PVE can further improve left lateral segment hypertrophy and allow extended resection. However, it comes with a risk of reflux of embolic material to segment II-III FLR portal veins. An alternative would be to perform liver venous deprivation with right and middle hepatic vein embolization at the same time. Early results from the ongoing HYPERLIVE01 trial are encouraging<sup>[96]</sup>. Patients should be monitored closely after PVE for potential complications, including liver failure, portal vein thrombosis and infection. Imaging should be performed to assess the extent of FLR hypertrophy and monitor tumour progression. There is no clear consensus regarding the timing of the scan, but a 4-6-wk window is preferred.

Based on the current evidence, PVE<sup>31</sup> should be considered as a treatment option for patients with hCCA who are not suitable for upfront curative resection but have a chance of achieving resectability with liver hypertrophy. After PVE, if the FLR remains < 20%, liver resection is deemed to be contraindicated.

In the case of biliary dilatation, biliary drainage should be performed before embolization<sup>[97]</sup>. Further research is needed to determine the optimal technique of PVE, the predictors of FLR hypertrophy and the effect of PVE on tumour progression and survival outcomes.

### *Recommendations*

**Recommendation 19:** PVE should only be performed in patients who can achieve resectability with liver hypertrophy (LoE 2; strong recommendation).

**Recommendation 20:** PVE should be considered in patients whose FLR<sup>23</sup> is less than or equal to 20% of total liver volume (LoE 2; strong recommendation).

**Recommendation 21:**<sup>23</sup> In patients with biliary dilatation of the FLR, a biliary drainage catheter should be placed before PVE (LoE 2, recommendation strong).

### **PREOPERATIVE BILIARY DECOMPRESSION**

Liver resection for hCCA carries mortality rates between 6.2% and 15.0%, with postoperative morbidity touching around 60% in Western studies<sup>[98-101]</sup>. Mortality is linked to postoperative hepatic insufficiency and sepsis, which develops in the compromised liver by previous jaundice, cholangitis and malnutrition<sup>[100-102]</sup>. The role of preoperative biliary drainage (PBD) in hCCA remains debated. The PBD<sup>25</sup> improves coagulopathy, alleviates renal insufficiency associated with liver failure and provides symptomatic relief<sup>[103]</sup>. The PBD reduces the risk of cholangitis and postoperative liver failure<sup>[104]</sup>. However, on the contrary,<sup>30</sup> cholangitis represents the most important

complication related to PBD and is an independent prognostic factor for postoperative mortality<sup>[98,102,105,106]</sup>.

While certain centres propose PBD until the serum bilirubin level descends below 2-3 mg/dL, optimal bilirubin levels before surgical resections remain variable across centres<sup>[60,107-110]</sup>. She *et al*<sup>[111]</sup> reported that a cut-off preoperative bilirubin level of > 4.39 mg/dL was associated with more hospital deaths (50.0% *vs* 8.5%;  $P = 0.004$ ) and 90-d mortality (50.0% *vs* 9.8%;  $P = 0.008$ ).

Biliary drainage of the FLR helps restore metabolic and synthetic liver function and minimizes the potential risk of atrophy due to chronic cholestasis. A study involving 287 patients at Memorial Sloan Kettering Cancer Centre and the Academic Medical Centre in Amsterdam also showed improved outcomes after PBD in patients with an FLR < 30%<sup>[99]</sup>. Major liver resection in 86 jaundiced patients without PBD with a predicted FLR of < 50% was associated with higher morbidity (55% *vs* 24%;  $P = 0.04$ ), mortality (23% *vs* 8%;  $P = 0.001$ ) and postoperative complications (62% *vs* 19%;  $P = 0.003$ )<sup>[112]</sup>. A meta-analysis assessing the efficacy of PBD in resectable hCCA involving 2162 patients favored PBD in patients with cholangitis, malnutrition (serum albumin < 3 g/dL), prolonged jaundice and high serum bilirubin levels  $\geq 15$  mg/dL<sup>[113]</sup>.

ERCP and percutaneous transhepatic biliary drainage (PTBD) are the most used modalities to achieve PBD for hCCA. The selection of drainage modality depends on local expertise, disease complexity, patient fitness and preferences. Giuliani *et al*<sup>[114]</sup> showed significantly higher failure rates of PBD at community hospitals than at referral centres (52.7% *vs* 36.9%;  $P = 0.002$ ).

Kishi *et al*<sup>[115]</sup> reported a higher incidence of major postoperative morbidities (Clavien-Dindo grade  $\geq$  III) in the PTBD (23%) *vs* non-PTBD (3%) groups ( $P = 0.01$ ). Wiggers *et al*<sup>[116]</sup> in a prediction model, reported that Bismuth-Corlette I & II resectable hCCA could benefit from ERCP as a primary drainage modality. In contrast, Bismuth-Corlette IIIa or IV hCCA and a total bilirubin level above 8.8 mg/dL may be considered for initial PTBD rather than ERCP. European Society of Gastrointestinal Endoscopy (ESGE) suggests that an MDT should decide the indication and route for PBD<sup>[117]</sup>.



DRAINAGE, a multicentre RCT, was prematurely terminated because of higher mortality (41% *vs* 11%;  $P = 0.03$ ) and cholangitis (59% *vs* 37%) in PTBD than in endoscopic biliary drainage (EBD) groups<sup>[118]</sup>. INTERCPT, another RCT, was also prematurely terminated due to higher mortality rates (50% EBD *vs* 80% PTBD)<sup>[119]</sup>.

Some studies advocate PTBD for its ability to drain specific liver sectors, though advancements in ERCP techniques enable sector-specific drainage in ERCP at experienced centres<sup>[120]</sup>. The endoscopic approach facilitates enteral drainage, resulting in improved nutritional status<sup>[121]</sup>. Tumour seeding is another concern requiring meticulous planning for appropriate drainage modality. The PTBD was an independent risk factor for seeding metastasis in patients with resectable hCCA than EBD<sup>[122,123]</sup>. A systematic review showed that EBD was superior to PTBD in the prevention of seeding metastasis (7.8% *vs* 17.1%, OR = 0.27, 95%CI: 0.13-0.56,  $P < 0.001$ )<sup>[124]</sup>.

Endoscopic drainage can be achieved by conventional plastic stents, the inside-stent technique, or endoscopic nasobiliary drainage. The latter is associated with fewer infectious complications but carries a greater risk of catheter dislocation. Data is scarce to recommend the utilization of fully covered self-expandable metal stents for PBD in resectable hCCA<sup>[125-130]</sup>.

The optimal extent of drainage remains controversial and functional liver volume is a better parameter to guide biliary drainage than the placement of unilateral or bilateral stents. Draining more than 50% of the liver volume is an independent factor contributing to improving hyperbilirubinemia with a lower incidence of cholangitis and prolonged survival<sup>[131-133]</sup>. The preferred drainage side remains the FLR for better peri and postoperative outcomes<sup>[101,134-138]</sup>.

There is no consensus about the optimal duration between PBD and surgical resection. Cholestasis impairs hepatic regeneration and restoration of hepatic function may take 4-6 wk after PBD<sup>[139]</sup>. Multiple factors influence the optimal timing of surgery, including improvement in bilirubin, cholangitis and nutritional status. Time duration varies across centres, ranging from 1 wk to 413 d between biliary drainage and surgery<sup>[113]</sup>.

## Recommendations

**Recommendation 22:** PBD of hCCA is not routinely recommended unless indicated in jaundiced patients with any of the following conditions (LoE 2; strong recommendation): Cholangitis, need for neoadjuvant therapy, preparation for PVEMalnutrition, hepatic or renal insufficiency, predicted FLR volume of  $\leq 30\%$  following surgery, and debilitating symptoms such as intense pruritus.

**Recommendation 23:** <sup>46</sup> The indication and route for PBD should be decided by an MDT based on patient characteristics, institutional experience, and resource availability (LoE 3; strong recommendation).

**Recommendation 24:** ERCP over PTBD is recommended for Bismuth-Corlette I and II, while the combination of ERCP and PTBD or PTBD alone is recommended for Bismuth-Corlette III and IV hCCA (LoE 3; weak recommendation).

**Recommendation 25:** PTBD is recommended in patients with unsuccessful and/or insufficient EBD (LoE 3; strong recommendation).

## SURGICAL RESECTION

<sup>18</sup> Surgical resection is the only potentially curative treatment option, with reported 5-year survival from 25%-40% in patients undergoing R0 resection<sup>[12,60]</sup>. Survival drastically decreases with involved resection margins and lymph node involvement<sup>[60,140]</sup>. Surgical resection should include complete excision of involved extrahepatic bile ducts with ipsilateral hepatectomy, caudate lobe resection<sup>[81,108,141-143]</sup>, lymphadenectomy<sup>[144]</sup>, hepaticojejunostomy and vascular resection<sup>[81,141,144]</sup> and reconstruction if required, aiming to obtain negative margins<sup>[60,144-146]</sup>. Limited resections of bile duct(s) are associated with increased recurrence and poor survival and are not recommended<sup>[141]</sup>. Hepatectomy can include right and left hepatectomy to right and left

trisectionectomies<sup>[12,81,141,143,144]</sup>. The standard treatment option for Bismuth-Corlette I & II tumour is right hepatectomy, with right-sided resection preferred due to the proximity of the right hepatic artery to the bile duct and the increased length of the extrahepatic portion of the left hepatic duct<sup>[147]</sup>. Left hepatectomy alone or accompanied by arterial resection and reconstruction of the right hepatic artery is considered in cases of insufficient functional hepatic reserve in case of right hepatectomy<sup>[89,148]</sup>, with large studies showing comparable long-term survival<sup>[83]</sup>. The choice of resection in Bismuth-Corlette III and selected cases of Bismuth-Corlette IV is dictated by the extent of biliary involvement, lobar atrophy, vascular involvement, side of biliary dominance and hilar anatomical variations with generally Bismuth-Corlette IIIa and IV requiring right trisectionectomy and Bismuth -Corlette IIIb and IV requiring left trisectionectomy.

Parenchymal sparing hepatectomies may be utilized in highly selected patients<sup>[81,141]</sup> as they are associated with an increased risk of positive surgical margins and decreased survival<sup>[144]</sup>. Concomitant pancreaticoduodenectomy may be included to obtain negative resection margins<sup>[146,149]</sup> as it can be accomplished with demonstrated safety in many reports and is associated with survival benefit<sup>[150]</sup>.

### *Staging laparoscopy*

This modality may be employed to exclude metastatic disease and avoid futile laparotomy<sup>[81]</sup>, but the practice remains optional<sup>[145]</sup>.

### *Extent of lymphadenectomy*

Regional lymphadenectomy should be performed in all patients undergoing surgical resection<sup>[60,86,141,144,151]</sup>. The 8<sup>th</sup> edition of the AJCC TNM staging system recommends the dissection of at least five lymph nodes for accurate staging<sup>[151]</sup>. The extent of lymphadenectomy remains controversial<sup>[151]</sup>, with Western studies recommending lymphadenectomy of the hepatoduodenal ligament<sup>[81]</sup> and lymph nodes posterior to the pancreatic head, *i.e.*, No. 12 and No. 13 lymph nodes<sup>[151]</sup> and inclusion of station 8 lymph nodes along common hepatic artery by Japanese studies<sup>[12,140]</sup>.

### *Frozen section*

Intraoperative frozen section analysis is preferred to obtain negative resection margins if further resection is possible<sup>[81,152]</sup>.

### *Recommendations*

**Recommendation 26:** Surgical resection should be offered to all potential candidates (LoE 2; strong recommendation).

**Recommendation 27:** The tumour should <sup>18</sup> be resected along with the involved biliary tree, ipsilateral hemi-liver, and caudate lobe with the aim of achieving a margin-negative resection (LoE 2; strong recommendation).

**Recommendation 28:** <sup>18</sup> Frozen section assessment of proximal and distal bile duct margins can be considered if further resection is possible (LoE 3; strong recommendation).

**Recommendation 29:** Hepatectomy with pancreaticoduodenectomy should be considered for positive resection margins (LoE 2; strong recommendation).

**Recommendation 30:** <sup>9</sup> Hepatectomy with portal vein resection and reconstruction should be considered in case of portal vein involvement (LoE 2; strong recommendation).

**Recommendation 31:** Hepatectomy with hepatic artery resection and reconstruction can be considered in case of hepatic artery involvement (LoE 2; weak recommendation).

## **LIVER TRANSPLANTATION**

While surgical resection remains the primary treatment for hCCA<sup>[81,153]</sup>, a significant majority present with irresectable disease, due to extensive biliary and vascular involvement at hepatic hilus and underlying parenchymal liver disease such as PSC<sup>[81,153]</sup>. Earlier attempts to employ orthotopic liver transplantation for such patients resulted in very dismal results<sup>[153-156]</sup>. This led to the development of combined protocols of neoadjuvant chemoradiation followed by liver transplantation in carefully selected patients<sup>[154]</sup>. The well-known Mayo Clinic Criteria<sup>[157]</sup> uses neoadjuvant chemoradiation along with diagnostic, inclusion and exclusion criteria, resulting in improved patient selection<sup>[155]</sup>. This was subsequently validated in a large multicentre cohort of 214 patients, using similar protocols of neoadjuvant treatment and a 5-year recurrence-free survival (RFS) of 65% was achieved<sup>[158,159]</sup>. At present, several transplant centres have approved protocols for liver transplantation in hCCA<sup>[153,154,159,160]</sup> and patients fulfilling Mayo criteria, after completing neoadjuvant chemoradiation, are awarded MELD exception points by UNOS in the United States<sup>[158,159]</sup>. On the contrary, this therapeutic option is not utilized in the United Kingdom, Germany, and Japan<sup>[159]</sup> due to the risk of recurrence under immunosuppression.

As discussed, the diagnosis of hCCA is challenging. In the setting of liver transplantation, the diagnosis of hCCA requires a dominant stricture of peri hilar ducts on imaging and one or more of the following: Positive endoscopic cytology or biopsy, fluorescent in situ hybridization polysomy, CA19-9 > 100 U/mL in the absence of obstructive jaundice<sup>[155,158]</sup>.

Liver transplantation with grafts retrieved from both cadaveric and living-related donors has been employed successfully<sup>[81,83,153-155,158,159]</sup>. Nevertheless, liver transplantation in hCCA is associated with higher rates of arterial and portal venous complications<sup>[156,159,161]</sup>. The neoadjuvant chemoradiation protocol has been modified by omitting brachytherapy to minimize the risk of hepatic artery thrombosis<sup>[159]</sup>. Successful liver transplantation may warrant the use of aorto-hepatic conduits<sup>[161]</sup> and interposition grafts for portal vein reconstruction<sup>[155,156,158,159]</sup>.



The outcomes of upfront liver transplantation for hCCA have been discouraging, with early recurrence and poor long-term survival<sup>[155,158,159]</sup>. Though established<sup>[155,158,159,162]</sup>, variability is found in components of neoadjuvant chemoradiation protocols<sup>[159,163]</sup> and the ideal protocol is to be defined<sup>[159]</sup>. However, a retrospective multicentre report from the European Liver Transplant Registry suggests that in carefully selected patients within the Mayo Clinic Criteria, 5-year survival of 60% could be achieved without neoadjuvant chemoradiation<sup>[164]</sup>, highlighting the significance of strict selection criteria<sup>[164]</sup>. This merits further exploration in clinical trials<sup>[164,165]</sup>.

### *Recommendations*

**Recommendation 32:** When considering liver transplantation for hCCA, the diagnosis requires the presence of a dominant stricture of peri hilar ducts on imaging and one or more of the following (LoE 2; weak recommendation): Positive endoscopic cytology or biopsy, positive fluorescent in situ hybridization polysomy, and CA19-9 <sup>33</sup> > 100 U/mL in the absence of obstructive jaundice.

**Recommendation 33:** For unresectable hCCA within Mayo Clinic Criteria, liver transplantation can be considered after neoadjuvant chemoradiation. The neoadjuvant regimen should include a combination of chemotherapy and radiation (LoE 2; weak recommendation).

**Recommendation 34:** Upfront liver transplantation can be carefully considered for hCCA, within the Mayo Clinic Criteria, if neoadjuvant treatment is not possible, only in centres with approved protocols (LoE 2; weak recommendation).

**Recommendation 35:** Given the increased vascular complications, the need for arterial and venous jump grafts (natural or synthetic) should be evaluated in preoperative liver transplant planning (LoE 2; strong recommendation).

## **ADJUVANT THERAPY FOR HCCA**

After complete surgical resection, almost 60% of patients in the high-risk group (*i.e.*, node-positive and/or margin-positive) develop local recurrence. Unfortunately, however, there is a dearth of RCTs providing high-quality data on the use of adjuvant treatments. Some studies have shown a lack of benefit of adjuvant treatment in low-risk groups, so these patients may be observed<sup>[166]</sup>. A retrospective study from MD Anderson Centre showed a 5-year survival of 36% and a locoregional recurrence rate of 38% in patients with positive resection margin or positive lymph nodes who received adjuvant chemoradiotherapy (CRT). On contrary, a 5-year survival of 42% and a locoregional recurrence rate of 37% was seen in patients with negative resection margin and negative lymph nodes with no adjuvant treatment<sup>[167]</sup>. A Korean study on patients treated with adjuvant radiotherapy showed a 5-year survival of 36%, 35%, and 0% in patients with negative margins, positive margins and gross residual disease, respectively<sup>[168]</sup>. Intention-to-treat analysis of the BILCAP study<sup>[169]</sup> showed a median overall survival (OS) of 49.6 months (95%CI: 35.10-59.10) in the patient group treated with adjuvant capecitabine compared with 36.1 months (95%CI: 29.70-44.20) in the observation group [adjusted hazard ratio (HR): 0.84; 95%CI: 0.67-1.06]. In the protocol-specified sensitivity analysis, adjusting for minimization factors, nodal status, grade and sex, the OS hazard ratio was 0.74 (95%CI: 0.59-0.94). The benefit of adjuvant therapy extended more to patients with margin-positive surgery and node-positive disease. A concise summary of the relevant clinical trials is provided in Table 4<sup>[169-171]</sup>.

### ***Recommendations***

**Recommendation 36:** For patients with resected, margin-negative hCCA with negative regional nodes, the following options are available based on local experience, available expertise and availability of drugs. Fluoropyrimidine (5 fluorouracil or capecitabine) or gemcitabine-based chemotherapy (LoE 2; weak recommendation). Fluoropyrimidine-

based chemoradiotherapy (LoE 2; weak recommendation). Observation (LoE 2; weak recommendation).

**Recommendation 37:** For patients with positive margins or positive regional lymph nodes include: Fluoropyrimidine- or gemcitabine-based chemotherapy (LoE 2; strong recommendation); fluoropyrimidine-based chemoradiotherapy (LoE 2; strong recommendation); and fluoropyrimidine or gemcitabine-based chemotherapy followed by fluoropyrimidine-based Chemoradiotherapy (LoE 2; strong recommendation).

## **SURVEILLANCE PROTOCOLS AFTER SURGERY/TRANSPLANTATION**

### ***Prognosis and surveillance after surgical resection***

Recurrent disease after surgical resection of hCCA is a foremost concern and is associated with poor prognosis. The major determinants of recurrence are resection margin status and lymph node metastasis<sup>[172-174]</sup>. Lymph nodal positivity and R1/2 resection are associated with early recurrence and poor survival outcomes<sup>[167]</sup>. The 5-year OS after hCCA resection ranges from 20%-42%<sup>[135,172-177]</sup>. In a recent systematic review and meta-analysis, Liang *et al*<sup>[174]</sup> extrapolated numerous factors that have prognostic value in determining the RFS and OS. The proven independent risk factors of OS are preoperative bilirubin levels (> 3 mg/dL), preoperative CA19-9 levels (> 150 U/mL), tumour size (2-3 cm), major vascular invasion, T-stage of disease (T3/4), lymph nodal metastasis (N-stage), moderate to poor tumour differentiation (grade 2 and 3), resection margin status, perineural and lymphovascular invasion<sup>[172-174]</sup>. Adjuvant chemotherapy has a positive impact on OS<sup>[174]</sup>. In a large retrospective study, Komaya *et al*<sup>[175]</sup> found that 5-year OS and RFS were significantly better in R0 resection than in R1 resection groups (48.5% *vs* 17.7% and 58.5% *vs* 10.4%, respectively). Further in-depth analysis revealed that 5-year RFS in the R0 resection group worsened as the number of poor prognostic factors increased<sup>[175]</sup>. Based on these observations, patients may be classified into high risk (R1 resection or R0 with one/more than one poor prognostic factors); and low risk (R0 resection with no risk factor).



Therefore, follow-up visits and postoperative treatment may be formulated based on identifying high-risk and low-risk groups after hCCA resection. As the high-risk group has a high chance of recurrence and poor OS, therefore; close surveillance is required<sup>[175]</sup>. The follow-up visit should include an assessment of clinical parameters, LFTs, tumour markers (CA19-9) and imaging at 2-3 monthly intervals for the first 2 years and then 6 monthly for up to 5 years. Imaging should include ultrasonography at each visit and contrast CT scan of the chest and abdomen or MRI at 6 monthly intervals or when clinical parameters mandate. These patients should be discussed in MDT meetings for adjuvant CRT for better outcomes<sup>[174]</sup>. A low-risk group should be followed with 2-3 monthly intervals for the first year, 6 monthly intervals for the second year and yearly for up to 5 years<sup>[178,179]</sup>.

### ***Prognosis and surveillance after liver transplantation***

Liver transplantation for unresectable hCCA in a selective cohort after neoadjuvant protocol demonstrates a promising overall outcome<sup>[155,158,178,180]</sup>. Although a significant body of literature demonstrates superior OS and RFS after liver transplantation for hCCA<sup>[155,156,158,162,180,181]</sup>, recent meta-analysis demonstrates the heterogeneity of these data in terms of patient selection (PSC *vs* non-PSC hCCA) and inherent limitations in study designs and data analyses resulting in wide variability in results<sup>[182]</sup>. Nonetheless, 5-year OS and RFS for patients undergoing liver transplantation after neoadjuvant protocol exceeds 50% and 65%, respectively<sup>[158,182]</sup>. Despite inconsistencies in outcomes, significant factors responsible for disease recurrence and patient survival are a response to neoadjuvant chemoradiation and residual disease in the explanted liver<sup>[156,181]</sup>.

In addition, the main outstanding issues in patients undergoing liver transplantation after neoadjuvant protocol are vascular (late hepatic artery thrombosis: 18.9% and portal vein thrombosis: 37.8%) and biliary complications (anastomotic stricture: 39.2%) as a consequence of irradiated porta hepatis<sup>[156,162]</sup>. This evidence supports the necessity of robust surveillance protocols. Thus, in addition to usual post-transplant surveillance,

a high-risk surveillance strategy for the detection of recurrence should be employed for those who have undergone liver transplantation.

### *Recommendations*

**Recommendation 38:** The high-risk group (R1 resection or R0 with one or more than one poor prognostic factor) should be followed every 3 months with clinical examination, CA19-9 and US. The CT scan should be done every 6 months for up to 5 years (LoE 2; weak recommendation).

**Recommendation 39:** The low-risk group (R0 resection with no risk factor) should be followed for 3 months with clinical examination, CA19-9 and ultrasound. The CT scan should be done for 6 months for the first year and then annually for up to 5 years (LoE 2; weak recommendation).

**Recommendation 40:** Post-transplant surveillance should follow a high-risk protocol (LoE 2; weak recommendation).

### **MANAGEMENT OF ADVANCED METASTATIC DISEASE**

Metastatic CCA carries limited treatment options and has a poor prognosis<sup>[183]</sup>. Systemic chemotherapy is the mainstay of treatment. Combination chemotherapy with cisplatin and gemcitabine has been the standard of care. It has shown an OS (HR: 0.64, 95%CI: 0.52-0.80;  $P < 0.001$ ) and median progression free survival (PFS) (HR: 0.63, 95%CI: 0.51-0.77;  $P < 0.001$ ) benefit compared to single agent gemcitabine in ABC-02 trial<sup>[184]</sup>. In patients with limited renal function, oxaliplatin may be substituted for cisplatin<sup>[185]</sup>. In the TOPAZ-1 trial<sup>[186]</sup>, a phase III RCT, the combination of cisplatin and gemcitabine was augmented with the programmed death-ligand 1 immune checkpoint inhibitor (ICI) durvalumab resulting in improved response rate, PFS and OS (primary endpoint; HR: 0.76, 95%CI: 0.64-0.91) compared to cisplatin and gemcitabine alone. Another similar study, KEYNOTE-966<sup>[187]</sup>, using pembrolizumab as an immunotherapy partner,

came to a similar conclusion. Median OS was 12.7 months (95%CI: 11.50-13.60) in the pembrolizumab group vs 10.9 months (95%CI: 9.90-11.60) in the placebo group (HR: 0.83, 95%CI: 0.72-0.95). Hence, this combination with ICI is considered the first-line treatment for advanced biliary tract cancers (BTC). The availability and cost of ICI are challenging in low-middle-income countries like Pakistan. Therefore, these medicines can be discussed on a case-to-case basis, especially in patients who are PDL-1 positive or have high microsatellite instability.

Molecular analysis should be carried out before or during first-line therapy to evaluate options for second and later lines of treatment in advanced disease. Approximately 40% of patients with BTC harbor genetic alterations, which are potential targets for precision medicine<sup>[188]</sup>. Fibroblast growth factor receptor (FGFR) or isocitrate dehydrogenase 1 (IDH1) inhibitors may be incorporated for patients with FGFR or IDH alterations<sup>[189,190]</sup>. Immunotherapy with ICIs has shown promise in a subset of patients with high microsatellite instability or mismatch repair-deficient tumours<sup>[191]</sup>. Palliative care should be integrated early in the treatment plan to address symptoms, improve quality of life, and provide psychosocial support. Close monitoring of treatment response and regular reassessment of the treatment strategy is essential, considering the dynamic nature of metastatic CCA and the potential for subsequent treatment modifications or clinical trial enrollment.

### *Recommendations*

**Recommendation 41:** ICIs are now incorporated in first-line regimens and should be used depending on availability with gemcitabine and cisplatin in metastatic CCA (LoE 2; strong recommendation).

**Recommendation 42:** In patients with FGFR alteration, FGFR inhibitors (*e.g.*, pemigatinib) should be considered as second-line therapy (LoE 3; weak recommendation).

**Recommendation 43:** Early integration of palliative care, focusing on symptom management, quality of life improvement and psychosocial support, is essential in the management of metastatic CCA (LoE 3, weak recommendation).

### PALLIATIVE CARE

Approximately 20%-30% of patients with hCCA are diagnosed at a stage when surgical resection can be offered. Furthermore, comorbidities preclude surgical resection in a significant number of patients. The median survival after resection can be up to 4 years; without resection, it is less than one year<sup>[192]</sup>.

For patients with a good performance status who have hyperbilirubinemia despite stenting, a non-gemcitabine-based regimen such as leucovorin-modulated fluorouracil (5-FU), or a fluoropyrimidine plus oxaliplatin such as FOLFOX or CAPOX, infusional 5-FU is recommended. Objective response rates for 5-FU alone or 5-FU based combination therapies range from 0 to 34 percent, median survival is usually 6 months<sup>[193]</sup>. For patients with a borderline performance status or extensive comorbidity, options include leucovorin-modulated 5-FU or single-agent capecitabine<sup>[194]</sup>.

Other locoregional therapies, such as photodynamic therapy, radiofrequency ablation, trans-arterial chemoembolization (TACE), drug-eluting bead TACE, selective intraarterial radiotherapy with 90-Y microspheres and external beam radiation therapy are available. However, no prospective, RCTs have shown a survival benefit with these therapies<sup>[195,196]</sup>. Supportive care helps patients meet the physical, practical, emotional, and spiritual challenges of cancer. It is essential to cancer care, especially after treatment has ended. The end of cancer treatment may bring mixed emotions. Even though treatment has ended, patients need help for pain, jaundice, loss of appetite, cholangitis, liver abscess and liver failure. The majority of these patients are candidates for palliative treatment<sup>[41,197-199]</sup>. The main aim of palliative treatment is to improve the quality of life by minimizing the number of hospitalizations. One of the main goals of palliation is to eliminate obstructive jaundice caused by the tumour, which can be achieved by PTBD or endoluminal stent therapy.

With all the recent advancements in interventional endoscopy and radiology, palliative therapy for patients with advanced hCCA is still suboptimal. Ashat *et al* reported that draining more than 50% of the liver volume is an important predictor of treatment effectiveness<sup>[200]</sup>. Given the significant morbidity and mortality related to recurrent cholangitis, meticulous optimization of biliary drainage is critical to improving survival rates in patients with advanced hCCA<sup>[201]</sup>.

The superiority of self-expanding metal stents (SEMS) compared to plastic stents in unresectable hCCA has been observed in several studies<sup>[202,203]</sup>. In a meta-analysis, SEMS had a lower risk of stent occlusion from sludge compared to the plastic stent [RR (95%CI): Uncovered SEMS *vs* plastic stent, 0.09 (0.04-0.18); and covered SEMS *vs* plastic stent, 0.17 (0.08-0.37)]<sup>[204]</sup>. Self-expanding metal stents are hence preferred in patients with life expectancy of > 3 months<sup>[205]</sup>.

The majority of studies on the natural progression of hCCA without any cancer treatment are retrospective in design and a large number of the patients who were treated with only best supportive care (BSC) had advanced cancer with a poor performance status (performance status 3-4)<sup>[192,206,207]</sup>. In a Korean study on BTC with BSC, the OS for intrahepatic, extrahepatic and ampulla of Vater cancer was 4.7 months, 9.7 months and 11.2 months respectively<sup>[208]</sup>. In multivariate analysis, variables associated with poor prognosis were metastatic biliary cancer (HR: 2.19,  $P = 0.001$ ), high baseline CEA level, defined as > 4.0 ng/mL (HR 1.51,  $P = 0.024$ ) and high baseline CA19-9 > 100 U/mL (HR: 1.93,  $P = 0.001$ )<sup>[208]</sup>.

### Recommendations

**Recommendation 44:** Palliative biliary drainage should be attempted at hepatobiliary centres (LoE 3; strong recommendation).

**Recommendation 45:** Biliary drainage offers significant survival benefits. The goal of drainage should be normalization and not just improvement of bilirubin levels (LoE 4; weak recommendation).



**Recommendation 46:** SEMS should be preferred for palliative drainage in those with life expectancy > 3 months (LoE 3; strong recommendation).

**Recommendation 47:** Patients who have advanced hCCA with high bilirubin and poor performance status of 3-4 should be offered supportive care (LoE 2, strong recommendation).

### **CONCLUSION**

Given the complexity of diagnosis and staging, each case of suspected hCCA should be discussed in a MDT meeting regarding surgical resection, tissue diagnosis, PBD, PVE and palliative drainage. Surgical resection remains the curative option. Immunotherapy is gaining prominence and presents a potential for enhanced survival in cases of unresectable hCCA.

### **ACKNOWLEDGEMENTS**

Dr Imran Ali Syed provided assistance during revision of the manuscript. Dr Amjad Zafar, Dr Kaleem ullah and Muhammad Khawar Shahzad attended the consensus meeting and provided valuable input.

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## Figure Legends

**Figure 1 Anatomical classification of hilar cholangiocarcinoma with International Classification of Diseases-11 codes.** CCA: Cholangiocarcinoma.

**Figure 2 Bismuth-Corlette classification.** Type I: Below the confluence of left and right hepatic ducts; Type II: Reaching confluence but not involving left or right hepatic ducts; Type III: occluding common hepatic duct and involving either the right (IIIa) or left (IIIb) hepatic duct; Type IV: Involving the confluence of both right and left hepatic ducts; bilateral intrahepatic segmental involvement or multicentric.

**Table 1 Level of evidence based on the Oxford Centre for Evidence-based Medicine (adapted from The Oxford 2011 Levels of Evidence)**

Level	Criteria	Simple model for high, intermediate, and low evidence
1	SR (with homogeneity) of RCT	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	RCT or observational studies with dramatic effects; SR of lower quality studies ( <i>i.e.</i> , non-randomised, retrospective)	
3	Non-randomised controlled cohort/follow-up study/control arm of randomised trial (systematic review is generally better than an individual study)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (AR is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain

RCT: Randomised controlled trials; SR: Systematic reviews; AR:

**Table 2 Grades of recommendation**

<b>Grade</b>	<b>Wording</b>	<b>Criteria</b>
Strong	Shall, should, is recommended. Shall not, should not, is not recommended	Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility
Weak or open	Can, may, is suggested. May not, is not suggested	

**Table 3 Risk factors for hilar cholangiocarcinoma**

Established	Less established	Potential (inconclusive data)
PSC	Inflammatory bowel disease likely <i>via</i> PSC	Obesity
Choledochal cysts	Cirrhosis	Tobacco smoking
Parasitic infections	Hepatitis B and C viruses	Genetic polymorphisms
Hepatolithiasis and	Diabetes	
Choledocholithiasis	Heavy alcohol use	
Toxins (Thorotrast contrast agent)	IgG4 related cholangitis	
	Abnormal junction between the common bile duct and pancreatic duct	
	Helicobacter bilis	
	Chronic typhoid infection	

PSC: Primary sclerosing cholangitis.



**Table 4 Clinical trials of adjuvant treatment in hilar cholangiocarcinoma**

Study	Design	Sample size	Treatment	Control	Key findings
JCOG1202, ASCOT	Phase 3	Total: 440; CCA: 180	S-1 <sup>1</sup>	Observation	3 yr OS: 77.1% vs 67.6% (95%CI: 61.0%- 73.3%); 3 yr RFS: 62.4% vs 50.9% (95%CI: 44.1%-57.2%)
BILCAP	Phase 3	Total: 447; CCA: 284	Capecitabine, duration: 6 months	Observation	OS (months): 51.1 vs 36.4 (95%CI: 34.6%- 59.1%); RFS (months): 24.4 vs 17.5 (95%CI: 18.6%-35.9%)
SWOG S0809	Phase 2	Total: 79; CCA: 53	GEMOX, duration: 4 cycles, followed by CRRT	None	Median OS: 35 months (R0, 34 months, R1, 35 months)

<sup>1</sup>S-1 is available only in Japan.

OS: Overall survival; 95%CI: 95% confidence interval; RFS: Recurrence-free survival;

CCA: Cholangiocarcinoma; CRRT: Concomitant chemoradiation therapy.

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