Consensus

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Chinese multicenter expert consensus on the diagnosis and treatment of hilar cholangiocarcinoma: 2025 edition

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SUMMARY: Hilar cholangiocarcinoma (hCCA) is a malignant tumor originating from the epithelial cells of the bile ducts, and it is characterized by an aggressive nature, complex surgical management, high mortality, and poor prognosis. Despite recent advances in surgical techniques, medical devices, and related technologies, there remains a pressing need to standardize diagnostic and therapeutic pathways to improve treatment outcomes and extend long-term patient survival. To better integrate and refine these standards, this consensus was reached through a national conference held in Changsha, Hunan Province, involving multidisciplinary experts from various regions across China. This collaborative effort, drawing from various medical facilities and academic organizations nationwide, resulted in the reaching of the "Chinese Multicenter Expert Consensus on the Diagnosis and Treatment of Hilar Cholangiocarcinoma: 2025 Edition" based on current clinical studies and over 40 years of clinical practice experience in managing hCCA. The consensus provides a comprehensive overview of hCCA, including its epidemiological characteristics, diagnostic and screening methods, pathological features, staging and classification systems, and various treatment modalities, while offering specific and actionable recommendations for clinical practice that highlight well-defined indications for surgical, local, and systemic therapies and that emphasize the importance of multidisciplinary approaches to both diagnostic and therapeutic workflows.

Keywords: hilar cholangiocarcinoma, diagnosis and treatment consensus, multidisciplinary approach, surgical management, biliary tract cancer

1. Introduction

Hilar cholangiocarcinoma (hCCA), also known as proximal cholangiocarcinoma, refers to cholangiocarcinoma arising from the bile duct epithelium between the confluence of the cystic duct and the common bile duct and the second-order bile ducts. It predominantly involves the left and right hepatic ducts, the bifurcation of the common hepatic duct, and the common hepatic duct itself. As the most prevalent biliary tract malignancy (accounting for approximately 40-60% of cases) (*1,2*), hCCA presents major therapeutic challenges due to its predilection for invading critical hilar structures, including blood vessels, neural plexuses, lymphatic tissues, and adjacent hepatic parenchyma (*3*). Curative-intent resection with microscopically negative margins (R0) remains the only potentially curative modality; however, approximately two-thirds of patients present with unresectable disease at initial diagnosis or surgical exploration (*4*). Comprehensive preoperative assessment and multidisciplinary treatment are critical to achieving optimal outcomes in patients with hCCA.

2. Methods

The Hepatobiliary Surgery Professional Committee of the Hunan Medical Association, the Hunan Provincial Clinical Research Center for the Prevention and Treatment of Biliary Diseases, the Hunan Provincial Key Laboratory for the Prevention and Treatment of Biliary Diseases, the Hunan Provincial Engineering Research Center for Digital Hepatobiliary Medicine, the Hepatobiliary Surgery Professional Committee of the Hunan International Medical Exchange and Promotion Association, the Hunan Alliance of Hepatobiliary and Pancreatic Surgery, the Hunan Alliance for the Diagnosis and Treatment of Malignant Biliary Tumors, and the Hepatopancreatobiliary Disease Research Center of the Furong Laboratory assembled multidisciplinary experts to systematically compile the latest evidence on hCCA diagnosis and treatment, incorporating over 40 years of clinical practice to draft the "Chinese Multicenter Expert Consensus on the Diagnosis and Treatment of Hilar Cholangiocarcinoma: 2025 Edition". This consensus emphasizes precise preoperative evaluation and the formulation of individualized treatment plans, while also highlighting the need for meticulous intraoperative techniques to enhance surgical quality and improve overall prognosis.

The consensus drafting process was initiated in early March 2024. From May to June 2024, the draft underwent rigorous review and discussion by an expert audit panel, with multiple revisions implemented during this period. On November 1, 2024, all members of the consensus committee convened in Changsha for the finalization meeting, where voting was conducted to establish consensus recommendations and their respective evidence grades, culminating in the finalized document. To systematically review recent advances in hCCA, the consensus committee implemented a comprehensive literature search strategy across multiple databases: PubMed, MEDLINE, EMBASE, Cochrane Library, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), and Wanfang Database. Search terms included: Hilar Cholangiocarcinoma, Epidemiology, Diagnosis, Pathology, Staging, Multidisciplinary Treatment, Surgery, Local Therapy and Systemic Therapy. Eligible studies encompassed systematic reviews, meta-analyses, randomized controlled trials (RCTs), cohort studies, and case-control studies addressing hCCA epidemiology, diagnostic approaches, therapeutic

Table 1. Levels of evidence quality

Level	Content
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with low risk of bias.
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
2++	High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies demonstrating minimal confounding or bias risk and a high likelihood of causality.
2+	Well-conducted case-control or cohort studies demonstrating minimal confounding or bias risk and a moderate likelihood of causality.
2-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk of no causal relationship.
3	Non-analytical studies, such as case reports or case series.
4	Expert opinions

Table 2. Levels of recommendation

Level	Definition
A	At least one meta-analysis, systematic review, or RCT rated as 1++, directly applicable to the target population; or evidence primarily from studies rated as 1+, directly applicable to the target population, demonstrating overall consistency in results.
B	Evidence includes studies rated as 2++, directly applicable to the target population; or studies rated as 2+, directly applicable to the target population and demonstrating overall consistency in results; or evidence extrapolated from studies rated as 1++ or 1+.
0	Evidence of level 3 or 4; or evidence extrapolated from studies rated as 2++ or 2+.
GPP	Good Practice Points (GPP): Best practices recommended by the guideline development group based on clinical experience.

interventions (surgical, local, and systemic), pathological characteristics, staging systems, and multidisciplinary treatment. Exclusions comprised basic research, brief communications, conference abstracts, and other low-evidence-level publications. The consensus adopted the Scottish Intercollegiate Guidelines Network (SIGN) (*5*) framework for evidence classification (Table 1). Recommendations were categorized into four levels (A, B, 0, and GPP) based on evidence quality (Table 2). A formal voting system was implemented to determine consensus levels: strong consensus, consensus, indeterminate opinion, and no consensus. An expert consensus was established if the ratio of a strong consensus and a consensus was ≥ 75% (Table 3).

Table 3. Classification of consensus strength

Level	Content
Strong consensus	> 90% of participants agree.
Consensus	75-90% of participants agree.
Indeterminate opinion	50-75% of participants agree.
No consensus	< 50% of participants agree.

Consensus Text

3. Epidemiology of and risk factors for hCCA

hCCA primarily occurs in individuals ages 50 to 70 years, with a male-to-female ratio of approximately 1.4:1 (*6-8*). The incidence of hCCA exhibits significant geographic heterogeneity. In Europe, the United States, and Australia, incidence ranges from 0.35/100,000 to 2/100,000. In contrast, regions where hepatobiliary flukes are endemic, such as Thailand, China, and South Korea, have a particularly high incidence, reaching 85/100,000 in Northeastern Thailand. The geographic heterogeneity of incidence probably reflects different underlying risk factors. In Western countries, primary sclerosing cholangitis (PSC) is the most prevalent risk factor for hCCA, while in Southeast Asia, hepatobiliary fluke infections predominate (*7*). Other established risk factors include congenital bile duct dilatation, hepatolithiasis, choledocholithiasis, liver cirrhosis, and chronic hepatitis B and C virus infections (*9,10*). A common characteristic of these risk factors is that they are associated with chronic inflammation of the biliary epithelium and cholestasis (*10*).

4. Screening and diagnosis of hCCA

4.1. Clinical manifestations

Patients with hCCA are usually asymptomatic in the early stages and may be incidentally detected during liver function tests or imaging studies performed for other reasons. Obstructive jaundice is the most frequent symptom of advanced disease, occurring in up to 90% of patients, and is characterized by progressive skin and sclera icterus, clay-colored stools, dark tea-colored urine, and pruritus. Other symptoms of advanced disease include abdominal pain, malaise, asthenia, anorexia, and weight loss. Approximately 10% of patients may develop concurrent biliary tract infection, presenting with right upper abdominal pain, fever, and jaundice (*11-13*).

4.2. Laboratory results

In cases of obstructive jaundice, liver function tests typically reveal elevated direct bilirubin levels. Alkaline phosphatase and gamma-glutamyl transferase levels usually rise in conjunction with bilirubin levels. In addition, some patients may also have elevated transaminases levels (*2*). Additional blood tests can be used to detect evidence of infection, particularly in cases of biliary obstruction (*e.g.*, elevated white blood cell count, neutrophilia, elevated C-reactive protein, and positive blood or bile cultures) (*12*).

Carbohydrate antigen 19-9 (CA19-9) is the most commonly used tumor marker for hCCA, with elevated levels observed in up to 85% of patients. Approximately 10% of patients lack the Lewis antigen and do not secrete CA19-9 (*14*). Elevated CA19-9 levels can also occur in biliary obstruction, pancreatitis, cirrhosis, hepatocellular carcinoma, and pancreatic cancer, resulting in a low positive predictive value (16–40%) (*13,14*). Despite these limitations, CA19-9 remains an important auxiliary diagnostic marker for hCCA. Persistent elevation after effective biliary drainage strongly suggests malignancy. Moreover, elevated serum CA19-9 levels in patients after radical surgery serve as an independent prognostic factor for disease recurrence and poor outcome (*15,16*). Carcinoembryonic antigen (CEA) is also a commonly used tumor marker for hCCA. Combining CA19-9 and CEA for screening in high-risk populations is recommended (*17*). Notably, approximately 15% of patients undergoing surgery for suspected hCCA are ultimately diagnosed with benign lesions, such as autoimmune cholangiopathy (*18,19*). IgG4-related sclerosing cholangitis, characterized by bile duct wall thickening, bile duct stricture, and obstructive jaundice, represents a critical differential diagnosis. Serum IgG4 levels are useful for distinguishing IgG4-related sclerosing cholangitis from hCCA (*20*).

Recommendation 1:

Liver function tests, CA19-9, CEA and IgG4 are recommended as baseline evaluations for suspected hCCA.

(1) While CA19-9 lacks specificity for hCCA and may be elevated due to obstructive jaundice, persistent elevation after effective biliary drainage strongly suggests malignancy.

(2) Combined detection of IgG4 aids in differentiating hCCA from IgG4-related sclerosing cholangitis. [Evidence Level: 1-, Recommendation Grade: A]

5. Imaging studies

Imaging studies play a pivotal role in the screening, diagnosis, staging, resectability evaluation, treatment assessment and follow-up of hCCA. Imaging assessments should include the extent of tumor axial spread along the bile duct tree, radial invasion beyond the bile duct wall, the relationship between the tumor and the portal vein and hepatic artery, regional lymph node metastasis, neural plexus infiltration, as well as intrahepatic and distant metastasis (*21*). The two primary pieces of radiological evidence for hCCA diagnosis are biliary obstruction and tumor mass.

Currently, the imaging modalities commonly used to reveal hCCA include non-invasive techniques such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), and positron emission tomography-computed tomography (PET/CT). In addition, there are invasive diagnostic approaches such as endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), cholangioscopy, and endoscopic ultrasonography (EUS). Performing CT or MRI before biliary decompression or an endoscopy is recommended to avoid secondary inflammation, stents, or other procedural factors that may affect the accurate assessment of the tumor (*22*). The diagnostic algorithm for hCCA is shown in Figure 1.

5.1. Ultrasound

Ultrasound is the preferred initial screening method for hCCA and is characterized by its convenience, speed, cost-effectiveness and non-invasiveness. Sonographic findings typically include intrahepatic bile duct dilation with abrupt truncation at the hilum, occasionally demonstrating intraluminal tumor echoes. Doppler ultrasound provides additional value in evaluating hepatic artery and portal vein involvement. However, ultrasonography has limitations in determining the location of obstruction, differentiating benign from malignant lesions, and evaluating the extent of tumor involvement. Enhanced CT and MRI need to be combined for further confirmation of the diagnosis (*23*). The diagnostic accuracy of ultrasonography may be compromised by technical factors such as abdominal wall adiposity or bowel gas interference, so its principal clinical utility thus lies in initial screening. Additionally, ultrasound can be used to guide percutaneous biopsy or biliary drainage procedures.

5.2. CT

CT is routinely used as the standard imaging modality with which to initially identify hCCA, and the scan includes the chest, abdomen, and pelvis. Its main advantage is the excellent spatial resolution, providing comprehensive assessment of the primary tumor, its local vascular relationships, and overall resectability. It also allows detection of local lymph adenopathy and metastatic disease, although it is less sensitive than PET/CT (*24-26*). A meta-analysis including 448 patients from

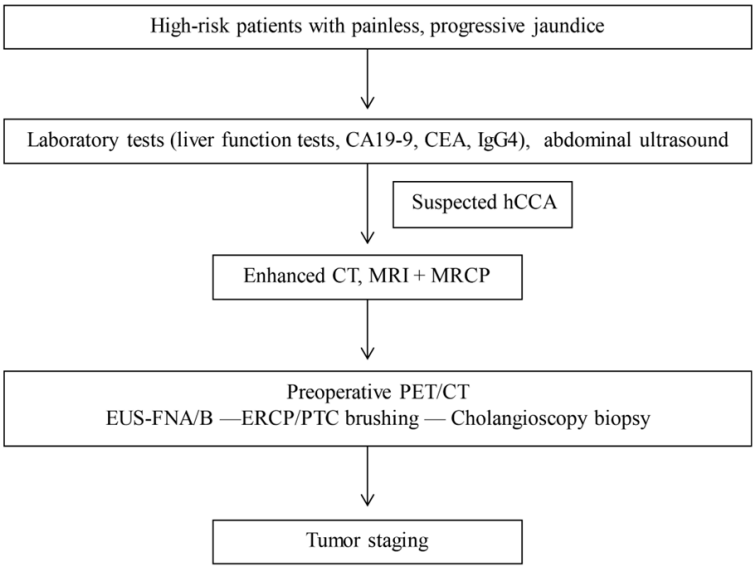

Figure 1. Diagnostic workflow for hCCA.

16 studies revealed that CT had a sensitivity of 89% and specificity of 92% for assessing portal vein involvement and a sensitivity of 83% and specificity of 93% for assessing hepatic artery involvement (*27*). In comparison, CT had a relatively lower accuracy in identifying lymph node metastasis (a sensitivity of 61%, a specificity of 88%) and distant metastasis (a sensitivity of 67%, a specificity of 94%). In contrast, PET/CT is superior at detecting distant metastasis, achieving a detection rate as high as 100% (*28*). Assessment of the extent of biliary involvement can also be difficult with CT, and particularly the proximal extent of perihilar tumors. Related studies have demonstrated that three-dimensional reconstruction of the bile ducts can improve the accuracy in evaluating the extent of bile duct involvement (*24,29*). Typical CT manifestations of hCCA include strictures at the major ductal confluence, accompanied by irregular wall thickening. CT generally displays progressive delayed enhancement and dilation of the upstream bile ducts (*30*).

5.3. MRI

MRI has advantages such as no radiation exposure, superior soft tissue resolution, and multi-parametric imaging. Moreover, hepatocyte-specific contrast agents can enhance the sensitivity of detecting intrahepatic micrometastases (*31*). MRCP provides unique diagnostic value for the biliary system, clearly displaying the biliary tree and depicting hilar obstruction and upstream biliary dilation. Abdominal contrast-enhanced MRI combined with MRCP can accurately show the primary tumor, biliary obstruction, vascular invasion, as well as regional lymph node metastasis and intrahepatic metastasis (*22*). hCCA lesions typically present with slight hyperintensity on T2-weighted imaging (T2WI), hypointensity on T1-weighted imaging (T1WI), hyperintensity on diffusion-weighted imaging (DWI), and progressive enhancement during contrast-enhanced scanning (*32*). Integrating MRI with MR angiography enables non-invasive vascular assessment comparable to conventional angiography (*33*). The available literature has indicated that the accuracy of contrast-enhanced MRI in association with MRCP is comparable to that of direct cholangiography *via* ERCP or PTC in differentiating benign from malignant obstruction, as well as the degree of extension. The presence of a long stenotic segment with thick and irregular margins, asymmetric narrowing, lumen irregularity, enhancement during the portal phase, a mass of periductal soft tissue, and nodal enlargement is suggestive of hCCA (*34*).

5.4. PET/CT

PET/CT is a functional imaging modality that has been found to play an important role in preoperative lymph node staging (N staging) and evaluation of distant metastasis (M staging) in hCCA. A prospective study found that PET/CT demonstrated superior N-stage accuracy (76%) compared to conventional CT alone (60%)(*35*). Another study revealed that PET/CT was able to detect occult metastatic lesions, leading to treatment strategy modifications in 30% (11 of 36) of patients (*36*). Nevertheless, PET/CT exhibits reduced sensitivity for small masses or periductal infiltrating hCCA. False-positive results may occur in non-malignant conditions such as primary sclerosing cholangitis (PSC), biliary infections, or granulomatous diseases. Considering the high cost, as well as its limitations, PET/CT is not recommended as a routine imaging modality for the initial diagnosis of hCCA.

Current clinical uses of PET/CT primarily focus on metastatic surveillance, recurrence assessment, and comprehensive lymph node evaluation.

5.5. Invasive examinations

Invasive examinations encompass ERCP, PTC, cholangioscopy, and EUS. Direct cholangiography, including ERCP and PTC, provides clear visualization of the obstruction site, the extent of involvement, and the morphology of upstream bile ducts. It is commonly used in patients with unresectable hCCA to obtain cytology or tissue for pathological diagnosis and to manage obstructive jaundice (*17*). Due to the risk of bleeding and infection, direct cholangiography is not recommended as a routine diagnostic method. Cholangioscopy provides direct visualization and allows biopsy of strictured segments. By inserting the SpyScope through the working channel of a duodenoscope and utilizing SpyBite, specimens can be obtained with a sensitivity of 64%, and especially in cases where ERCP sampling is insufficient or biliary strictures are indeterminate (*27*). Anatomically, the extrahepatic bile ducts are located close to the duodenum. Thus, EUS enables detailed observation of the extrahepatic bile duct tree and its adjacent structures. A study has shown that EUS can detect metastatic lymph nodes not identified on conventional cross-sectional imaging, with a detection rate of 15–20% (*37*). Nevertheless, endosonographic morphology and echogenic characteristics cannot reliably predict malignant lymph node involvement, necessitating endoscopic ultrasound-guided fine-needle aspiration/biopsy (EUS-FNA/B) (*35*). A point worth noting is that EUS-FNA/B may increase the risk of tumor seeding. Therefore, it should be avoided when liver transplantation is considered a treatment option (*27,38*).

Recommendation 2:

For patients with suspected hCCA, enhanced chest, abdominal, and pelvic CT and/or enhanced MRI + MRCP are recommended to assess the primary tumor, its local vascular relationships, distant metastases, and overall resectability. [Evidence Level: 2+, Recommendation Grade: B]

Recommendation 3:

If biliary drainage is required, imaging should be performed before endoscopic nasobiliary drainage (ENBD), endoscopic retrograde biliary drainage (ERBD), or percutaneous transhepatic cholangial drainage (PTCD) to obtain high-quality imaging for tumor evaluation and to avoid inflammation or artifacts caused by interventions such as catheters or stents. [Evidence Level: 1-, Recommendation Grade: A]

Recommendation 4:

PET/CT is recommended for evaluating distant metastases, disease recurrence, lymph node metastases, and differential diagnosis when routine imaging is inconclusive for hCCA. PET/CT is not recommended as a routine imaging method for initial diagnosis. [Evidence Level: 2++, Recommendation Grade: A]

Recommendation 5:

Invasive procedures such as PTC, ERCP, cholangioscopy, and EUS can be utilized for pathological diagnosis in unresectable hCCA. Additionally, they can serve as complementary methods to other imaging techniques. Despite their potential therapeutic applications, such as in biliary drainage, these invasive procedures are nevertheless not recommended as routine diagnostic tools for suspected cases of hCCA. [Evidence Level: 2+, Recommendation Grade: B]

6. Pathological characteristics of hCCA

6.1. Methods of pathological diagnostic

Histopathological and/or cytological examination is the gold standard for diagnosing hCCA. For unresectable hCCA, pathological diagnosis is required to guide subsequent treatment and predict prognosis (*19,37*). For patients scheduled to undergo surgical resection, preoperative biopsy may be avoided due to its low sensitivity and risk of tumor dissemination (*17*). Most hCCAs are periductal-infiltrating carcinomas, so percutaneous biopsy is less often used to obtain tissue samples. ERCP, PTC, cholangioscopy, and EUS can provide channels for cytological brushing and biopsy (*39*). Due to the high fibrous stromal content of tumors, the cellular yield from brushing is limited, resulting in a low sensitivity for cytological brushing of approximately 30–60% (*39,40*). Therefore, combining cytological brushing with tissue biopsy is recommended to improve diagnostic sensitivity (*37*).

Current ERCP-guided sampling techniques require X-ray assistance. The procedure involves continuous cholangiography to visualize the operational pathway and location, without direct visualization of the biliary tract. Cholangioscopy systems enable transoral direct visualization of the biliary tract, enabling the assessment of biliary strictures and characterization of lesions. Studies have shown that the sensitivity, specificity, and accuracy of cholangioscopy in diagnosing malignant biliary strictures are 86.7-100%, 71.2-95%, and 77.2-95.1%, respectively (*41-43*). The SpyBite biopsy forceps, specifically designed for use with cholangioscopy, can be used to perform targeted biopsies under direct visualization, with a sensitivity of 63.6-86% and a specificity of as high as 100% (*41,43,44*). A study of 16 patients who underwent transabdominal fine-needle aspiration indicated that among six patients with adenocarcinoma confirmed by histological examination, five had peritoneal metastases

during surgery (*38*). When liver transplantation is considered as a treatment option, EUS-FNA/B should be avoided. Therefore, EUS-FNA/B and percutaneous puncture methods for biopsy are not recommended as initial diagnostic approaches for patients with malignant hilar strictures. Intraluminal sampling using multiple techniques (*e.g.*, brushing, biopsy forceps, and biopsy guided by a cholangioscope) during ERCP is preferred (*45*). EUS-FNA/B can be used to obtain biopsies of regional lymphadenopathy or for biopsy of the tumor site when ERCP or PTC-guided biopsies are negative or inconclusive (*13,19*). The optimal sampling method for patients should be selected based on the location and extent of the biliary stricture, the size of the mass, and the skills and experience of the operator, along with the method of biliary drainage and the risk of tumor dissemination.

Recommendation 6:

Given that approximately 15% of resected hilar specimens are benign (such as autoimmune cholangiopathy), histological or cytological confirmation is mandatory before initiating chemoradiotherapy for unresectable hCCA. Preoperative biopsy may not be necessary for resectable hCCA. In cases of unresectable lesions with multiple negative sampling results, the treatment plan should be determined through multidisciplinary team discussion. For potentially resectable hCCA, the decision to perform a biopsy should be made through multidisciplinary team discussion. [Evidence Level: 2+, Recommendation Grade: B]

6.2. Pathological subtypes

Most hCCAs originate from columnar mucinous cholangiocytes or peribiliary glands (*10*). Tumor grading should be based on the least differentiated component within the neoplasm, rather than the proportion of glandular components. According to glandular differentiation, mucin production, mitotic activity, and nuclear features, hCCA can be classified as well-differentiated, moderately differentiated, or poorly differentiated adenocarcinoma. In cases of histological heterogeneity, the worst grade should be reported (*46*). hCCA can also be classified into distinct morphologic subtypes termed by the Liver Cancer Study Group of Japan as periductal infiltrating, mass-forming, intraductal growing, and mixed subtypes. The periductal infiltrating type is the most common and is characterized by irregular thickening of the bile duct (*47*).

6.3. Immunophenotype and molecular features

hCCA shares similar pathological and molecular characteristics with large duct intrahepatic cholangiocarcinoma (iCCA) (*48,49*). Immunohistochemically, hCCA is typically positive for CK7 and CK19. Subtyping markers, including MUC5AC, MUC6, and S100P, are also frequently positive. The molecular landscape of hCCA is characterized by rare IDH mutations and FGFR fusions; a high frequency of KRAS and TP53 mutations, though the KRAS G12C mutation occurs in only about 1% patients, and frequent Her-2 amplification and SMAD4 loss of expression (*10,48,50*). Advances in precision medicine and genetic testing have identified more therapeutic targets. For unresectable or metastatic hCCA, relevant therapeutic targets should be tested for, such as HER2 overexpression or amplification, IDH1/2 mutations, FGFR2 fusions, BRAF V600E mutation, NTRK fusions, RET fusions, KRAS mutations, microsatellite instability (MSI), and PD-L1 expression (*17*).

Recommendation 7:

For patients with unresectable or metastatic hCCA, molecular testing should be conducted based on therapeutic needs, such as identification of HER2 overexpression or amplification, IDH1/2 mutations, FGFR2 fusions, BRAF V600E mutation, NTRK fusions, RET fusions, KRAS mutations, MSI, and PD-L1. [Evidence Level: 2-, Recommendation Grade: 0]

6.4. Key Points in pathological diagnosis

The most common type of hCCA is the periductal infiltrating type. For the periductal infiltrating and intraductal growing types, specimens should be obtained by longitudinal sectioning along the bile duct axis. These specimens should encompass the tumor, the adjacent liver tissue, and the bile duct wall. Measuring the length of the affected bile ducts, the thickness of the wall, and the shortest distance between the tumor and the margin is essential. Sampling should be performed at the junctions between the affected duct walls and the surrounding liver parenchyma, as well as at the ductal margins. For mass-forming hCCA, specimens should be collected following "7-point" baseline sampling (*51*). According to the International Collaboration on Cancer Reporting (ICCR) standards, pathology reports should include detailed descriptions of gross specimens, tumor location and number, size, length and thickness of the affected bile ducts, tumor type, histological grade, extent of local invasion, perineural and vascular invasion, lymph node status, margin status, precancerous lesions, and other associated conditions (*46*).

Recommendation 8:

Standardized pathological sampling should be performed. For the periductal infiltrating and intraductal growing types of hCCA, specimens should be obtained by sectioning along the long axis of the bile duct, including the tumor and adjacent liver tissue. For mass-forming hCCA, "7-point" baseline sampling should be used. Pathology reports should conform to ICCR standards to

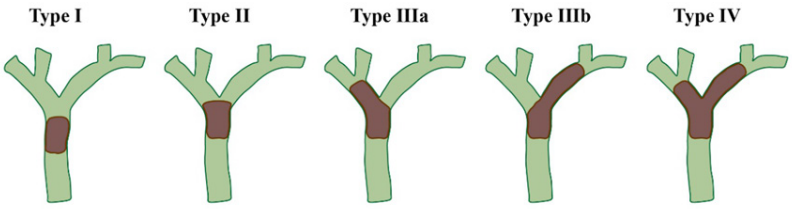

Figure 2. Bismuth-Corlette Classification of hCCA.

improve diagnostic consistency and uniformity. [Evidence Level: 3, Recommendation Grade: GPP]

7. Classification and staging of hCCA

Classification and staging of hCCA are crucial to guiding surgery and predicting prognosis. Currently, three widely used international classification/staging systems are available. However, due to the complex location and infiltrative nature of hCCA, these systems have certain limitations.

7.1. Bismuth-corlette classification

This classification was first proposed by Bismuth *et al*. in 1975 and, after several revisions, evolved into the widely used Bismuth-Corlette classification system in 1992 (Figure 2, Table 4). This classification is based on the location and extent of tumor involvement in the bile duct tree. It is simple and provides significant guidance for surgical planning. Though its efficacy has been proven, its limitation is its inability to predict the presence of distant metastases, lymph nodal and vascular involvement, and consequent lobar atrophy, and subsequently, patient survival (*52*).

Table 4. Bismuth-Corlette Classification of hCCA

Classification	Tumor Characteristics
Type I	Tumor in common hepatic duct
Type II	Tumor with confluence involvement
Type IIIa	Tumor with the confluence and right hepatic duct involvement
Type IIIb	Tumor with the confluence and left hepatic duct involvement
Type IV	Tumor invasion of bilateral intrahepatic secondary bile ducts

7.2. MSKCC staging system

The MSKCC (Memorial Sloan-Kettering Cancer Center) staging system (Table 5) evaluates hCCA based on tumor extent, portal vein invasion, and the presence of liver lobe atrophy. Its main purpose is to evaluate resectability. Since it incorporates two additional evaluation factors, namely portal vein invasion and liver lobe atrophy, it is superior to the Bismuth-Corlette classification in determining resectability. However, MSKCC staging does not take into account factors such as hepatic artery involvement, lymph node status, and distant metastasis, making its assessment less comprehensive (*53*).

7.3. American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM staging system

The TNM staging system (Table 6) aims to standardize staging with other malignancies. This classification system considers the size of the primary tumor (T), the number of regional lymph node metastases (N), and the size and extent of distant metastases (M). It is currently the most widely used clinical staging system and serves as a standard for evaluating prognosis. However, it primarily relies on pathological histological criteria, which are often difficult to determine preoperatively (*54*).

Recommendation 9:

The three commonly used international classification/staging systems for hCCA each have distinct advantages while also having certain limitations. The Bismuth-Corlette classification focuses on describing the anatomical location of the tumor, incorporating vascular and lymph node involvement to guide surgical planning. MSKCC staging evaluates resectability. The AJCC/UICC TNM staging system serves to guide postoperative treatment and assess prognosis. [Evidence Level: 3, Recommendation Grade: GPP]

8. Multidisciplinary treatment (MDT)

hCCA demonstrates aggressive biological behavior. It is frequently diagnosed in advanced stages and has a dismal prognosis. Patients are categorized into those with resectable, potentially resectable, or unresectable hCCA. For early-stage hCCA, surgery is preferred, aiming for an R0 resection. Potentially resectable hCCA cases where an R0 resection cannot be ensured have the following imaging features: (1) metastatic lymph nodes in the hepatoduodenal ligament or retroperitoneum; (2) involvement of the portal vein and/or hepatic artery, hepatic vein, or inferior vena cava, requiring vascular resection. For advanced or late-stage unresectable

Table 5. MSKCC staging system for hCCA

Classification	Tumor Characteristics
T1	Tumor involving biliary confluence +/- Unilateral extension to secondary bile duct root.
T2	Tumor involving biliary confluence +/- Unilateral extension to secondary bile duct root and ipsilateral portal vein involvement +/- ipsilateral liver lobe atrophy.
T3	Tumor involving biliary confluence + Bilateral extension to secondary bile duct roots/unilateral extension to secondary bile duct root and contralateral portal vein/unilateral extension to secondary bile duct root with contralateral hepatic lobe atrophy; Main portal vein or bilateral portal vein involvement.

Table 6. AJCC 8th TNM staging system for hCCA

Primary tumor (T)	Tx: The primary tumor cannot be evaluated. T0: No evidence of primary tumor. Tis: Carcinoma in situ. T1: Limited to bile ducts, reaching muscularis or fibrous tissue. T2a: Beyond the bile duct wall to the surrounding adipose tissue. T2b: Invasion of adjacent liver parenchyma. T3: Invasion of one branch of the portal vein or hepatic artery. T4: Invasion of the main portal vein or its bilateral branches, or common hepatic artery; or tumor invasion of one secondary bile duct into the contralateral portal vein or hepatic artery
Regional lymph nodes (N)	Nx: Regional lymph nodes cannot be determined. N0: No regional lymph node metastasis. N1: 1–3 regional lymph nodes involved. (Regional lymph nodes are defined as those distributed along the hepatic hilum, cystic duct, common bile duct, hepatic artery, portal vein, and posterior to the pancreaticoduodenal region). N2: ≥ 4 regional lymph nodes involved.
Distant metastasis (M)	M0: No distant metastasis. M1: Distant metastasis present (includes non-regional lymph nodes metastasis).
Staging	0 TisN0M0 I T1N0M0 II T2a-2bN0M0 IIIA T3N0M0 IIIB T4N0M0 IIIC any TN1M0 IVA any TN2M0 IVB any T any NM1

hCCA, the mainstay of management is systemic therapy, which includes chemotherapy, targeted therapy, and immunotherapy. These are often combined with localized treatments such as radiotherapy and interventional procedures. Given the limited efficacy of single-treatment modalities, the rational combination and sequential use of multiple therapeutic approaches are required. The MDT-based diagnostic and therapeutic model has become an essential strategy for prolonging survival in patients with complex hCCA. After completing imaging studies, MDT meetings should integrate the patient's medical history, clinical presentation, laboratory results, and imaging results to perform a comprehensive evaluation, determine disease staging, and formulate a rational treatment plan. The MDT expert consensus recommends the participation of specialties such as hepatobiliary surgery, medical oncology, radiology, interventional medicine, gastroenterology, radiotherapy, ultrasound, and pathology (*55*). The goal of MDT is to incorporate the latest advances in various specialties and the comprehensive patient profile, including disease stage, treatment needs, financial capacity, and psychological tolerance, to devise a more scientific, rational, and standardized therapeutic strategy. Additionally, it also supervises treatment implementation, regularly evaluates efficacy, and adjusts the strategy to maximize patient benefits (*56*).

Recommendation 10:

The MDT model has become an important strategy for prolonging survival in hCCA patients. An early MDT approach for complex hCCA cases is recommended to determine disease stage and potential treatment strategies. A rational combination and sequential use of multiple treatments are advised. [Evidence Level: 4, Recommendation Grade: GPP]

9. Surgery for hCCA

Currently, surgery is the only potentially curative treatment for hCCA, with the primary goal of achieving an R0 resection (*57*). However, the rate of non-R0 resections remains high. Adequate preoperative preparation

and standardized surgical planning are essential to accomplishing high-quality curative resections. Enhanced preoperative evaluations, including detailed disease stage and comprehensive assessment of physical condition, are recommended to improve surgical success rates and reduce postoperative complications. Postoperative follow-up should be conducted regularly based on pathological findings and recovery status, with additional therapies used as necessary.

9.1. Preoperative biliary drainage (PBD)

PBD is a critical component of the perioperative management strategy for hCCA patients. Jaundice is known to have detrimental effects on mitochondrial function, diminish immunity, impair intestinal barrier function, and increase the risk of bacterial translocation (*58*). The aim of PBD is to relieve obstructive jaundice, improve liver function, and prepare for curative surgery. Studies have demonstrated that PBD can reduce post-hepatectomy complications and promotes liver regeneration. However, it may also pose risks such as tumor seeding, prolonged hospitalization, morbidities, and infection(*59*). PBD is not recommended for all patients. Instead, it should be selectively considered under specific conditions: (1) presence of cholangitis; (2) preoperative preparation for portal vein embolization (PVE); (3) total serum bilirubin >200 μmol/L; (4) planned extensive hepatectomy with a future liver remnant (FLR) < 40%; (5) planned preoperative neoadjuvant/conversion therapy; and (6) poor physical condition or hepatic/renal insufficiency (*39,58,60-62*).

The associated controversies are the optimum level of bilirubin to be achieved, the duration of the drainage, and methods of drainage. The optimal level of serum bilirubin differs in various studies, with levels of 50 μmol/L and 85 μmol/L being the most common (*4*). The optimal duration of PBD remains unclear because of the risk of drain malfunction, inflammation surrounding the surgical field with subsequent increased anastomotic leaks, and tumor progression in the event of longer waiting times. In previous studies, the waiting period has ranged from 10 to 32 days, with complete normalization typically occurring around 4 to 8 weeks (*63*). There are three main methods of biliary drainage for hCCA: percutaneous transhepatic biliary drainage (PTBD), ERBD, and ENBD. However, no randomized trials have compared them. They all possess distinct advantages and drawbacks. At present, selection of the optimal method of drainage remains a subject of contention. Insufficient data exist to reach a universal consensus. A medical center can determine the method of drainage by performing a comprehensive multidisciplinary evaluation tailored to the patient's specific condition. Prior to decision-making, several key factors need to be taken into account, including the anatomical site of the obstruction, the intended goal of drainage, the availability of equipment at the medical center, the operator's experience and local skills, as well as the patient's preferences.

PBD is recommended in Western countries, and yet the precise method of drainage has yet to be clearly defined (*37*). The guideline suggests that hCCA patients scheduled for extensive hepatectomy should undergo PBD, with ENBD being the first choice and that preoperative serum bilirubin should be less than 50 μmol/L in Japan (*64*). Li *et al*. developed a short-cycle biliary drainage protocol (within 3 to 4 weeks) for performing PTBD on the planned residual liver lobe (*65*). This protocol adopts the criterion that the preoperative total serum bilirubin level of ≤ 85 μmol/L serves as an indication that liver reserve function can endure extensive hepatectomy. Moreover, it places significant emphasis on bile reinfusion. Within a relatively shorter period of drainage, PTBD does not elevate the risk of tumor seeding. This protocol has proven beneficial in shortening the preoperative preparation period and lowering the risk of cholangitis (*66*).

Recommendation 11:

Routine PBD is not recommended. Instead, PBD should be considered under the following specific conditions: (1) presence of cholangitis; (2) preoperative preparation for PVE; (3) total serum bilirubin >200 μmol/L; (4) planned extensive hepatectomy (FLR <40%); (5) planned preoperative neoadjuvant/conversion therapy; (6) poor physical condition or hepatic/renal insufficiency. [Evidence Level: 2+, Recommendation Grade: B]

9.2. PVE

The future liver remnant (FLR) is a critical factor in assessing tumor resectability and the risk of postoperative liver failure. Patients who fail to meet the required FLR threshold face a significantly increased risk of postoperative liver failure and mortality (*67,68*). Generally, an FLR of at least 20% is required for a normal liver, 30% for patients receiving chemotherapy, and 40% for cirrhotic patients (*69*). A study has indicated that the critical threshold of the future liver remnant volume-to-body weight ratio (FLRV/BW) for predicting postoperative complications, mortality, and liver failure is 0.5%. Patients with a FLRV/BW < 0.5% face significantly higher risks of these outcomes (*68*). Methods commonly used to induce FLR hypertrophy include PVE and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS).

PVE achieves FLR hypertrophy by embolizing the portal vein of the liver segment planned for resection, redirecting blood flow. It is indicated for patients with an insufficient FLR for surgery. PVE reduces surgical risks and provides an opportunity for patients with an insufficient FLR to undergo surgery, making it an effective preoperative strategy (*70,71*). PVE enables

the planned residual liver lobe to pre-adapt to the hemodynamic alterations in blood supply before surgery. By doing so, it mitigates the risk of liver failure caused by the sudden changes in portal venous blood supply and pressure within the residual liver lobe following extensive hepatectomy. A clinical study conducted in the Netherlands revealed that three weeks after PVE, the FLR not only grew, but liver function was also markedly enhanced. Moreover, the rate at which liver function improved exceeded the rate of the increase in liver volume (*72*). In healthy livers, FLR growth can typically be observed within 2 to 4 weeks following PVE. A study has indicated that the FLR increases by an average of 8% to 27% after PVE treatment (*73*). ALPPS can induce FLR hypertrophy. Nevertheless, complications such as postoperative infections and bleeding caused by the first-stage operation, as well as the impact of the second operation within a short period of time, lead to a persistently high incidence of complications and a high mortality rate among patients (*74,75*). In a case-control analysis of an international ALPPS registry, the mortality rate in the ALPPS group was twice that of the matched patients who received standard hepatectomy (48% *vs.* 24%) (*58*). Therefore, PVE can be regarded as the preferred approach for FLR hypertrophy.

There is no definitive criterion for when preoperative PVE is indicated for hCCA. The guideline recommends PVE for cases where the planned hepatectomy volume/liver total volume ratio is ≥50%–60% in Japan (*64*). The early expert consensus on hCCA in China suggests that PVE should be performed for patients undergoing extended hepatectomy (≥ 5 liver segments) (*76*). The consensus also recommends performing biliary drainage first to reduce serum total bilirubin levels below 85 μmol/L before proceeding with PVE.

<u>Recommendation 12:</u>

PVE is recommended for patients with anticipated FLR <30% before major liver resection, along with indocyanine green clearance (ICG) testing. FLR should be re-evaluated 2–4 weeks after PVE to enhance the likelihood of safe resection. [Evidence Level: 1-, Recommendation Grade: A]

9.3. Definition of radical resection

Radical resection of hCCA is defined as a pathologically negative margin (pR0) for all surgical specimens, including the bile duct, adjacent liver tissue, blood vessels, and soft tissues. Therefore, evaluating whether radical resection is achieved should not only rely on tumor-free bile duct margins but also include comprehensive dissection of soft tissue from the hepatoduodenal ligament to the hepatic hilum, achieving skeletonization of the portal vein and hepatic artery. Pathological analysis of surgical specimens must follow standardized sampling and processing protocols to enhance diagnostic accuracy (*77*).

ICCR recommends defining an R0 resection as having no cancer cell infiltration within 1 mm of the surgical margin, although evidence regarding its prognostic significance remains limited (*46*). Unlike most intrahepatic tumors with well-defined margins, accurately determining the tumor margins with the naked eye is sometimes difficult due to the growth characteristics of hCCA. Therefore, performing rapid intraoperative pathology to ascertain the nature of the bile duct resection margin is of great importance (*78*). A Japanese study found no significant difference in disease-free or overall survival (OS) between patients whose initial pR1 bile duct margins were converted to pR0 through re-resection and those whose margins remained pR1, both faring worse than patients with primary pR0 margins. Negative bile duct margins (pR0) should be achieved in a single attempt whenever possible (*79*). According to the literature, patients with an R1 resection have better survival than those with an R2 resection or those who are deemed inoperable. Therefore, palliative resection is recommended over conservative treatment for hCCA cases where an R1 resection is achievable (*80-82*).

<u>Recommendation 13:</u>

Maintaining the integrity of bile duct tumor resection is crucial for prognosis. Achieving negative margins (pR0) in a single attempt is recommended. According to the literature, an R1 resection offers better survival than an R2 resection or inoperability. For hCCA cases where an R1 resection is achievable, palliative resection is recommended over conservative management. [Evidence Level: 2+, Recommendation Grade: B]

9.4. Extent of hepatectomy

hCCA often presents with occult symptoms, and most cases are diagnosed in an advanced stage, requiring extended hemihepatectomy for curative surgery (*29*). The goal of surgery is an R0 resection, while preserving a sufficient FLR is a crucial preoperative consideration. Surgical approaches for Bismuth-Corlette type I and II hCCA are a subject of debate, particularly regarding whether to perform simple extrahepatic bile duct resection or to combine it with hepatic resection (*83*). Currently, the mainstream view holds that for Bismuth-Corlette type I and II tumors without vascular invasion, bile duct tumor resection with regional lymphadenectomy is sufficient for patients with Bismuth–Corlette type I and that it should be combined with caudate lobectomy for patients with Bismuth–Corlette type II. The rationale behind caudate lobe resection is that its duct drains near the hepatic confluence, which increases the risk of tumor involvement. Ruling out tumor involvement of the caudate lobe bile duct branch based solely on non-dilated imaging findings is difficult, and its resection improves

the rate of an R0 resection (*4,21,65,66,76*).

For Bismuth type III and IV hCCA, surgical strategies involve hemihepatectomy, central hepatectomy, or more extensive liver resection. For Bismuth IIIa hCCA, right hemihepatectomy combined with caudate lobe resection is recommended. For Bismuth IIIb hCCA, left hemihepatectomy combined with caudate lobe resection is advised (*4,13*). Bismuth type IV hCCA was once considered unresectable; however, recent advances allow curative resection in some patients through extended hemihepatectomy or trisegmentectomy combined with caudate lobe resection and vascular reconstruction (*84,85*). For type IV hCCA where the tumor on the right side spreads to the left side and invades the root of the bile duct of the left medial segment (S4), extended right trisegmentectomy combined with caudate lobe resection can be performed. For type IV hCCA where the tumor on the left side invades the right and involves the root of the bile duct of the right anterior lobe, extended left trisegmentectomy combined with caudate lobe resection can be performed.

For centrally located tumors, both extended right and left hepatectomy are viable treatments. The literature suggests similar survival and recurrence rates for both approaches; however, surgeons tend to prefer right hepatectomy due to various anatomical considerations, like the longer extrahepatic course of the left duct, the right-sided lie of the bile duct confluence, the right hepatic artery running behind the common duct with the risk of tumor involvement, and anatomical variations being more likely on the right side, which may preclude a safe left hepatectomy. Right-sided resections have a higher incidence of posthepatectomy liver failure in comparison to the left-sided resections. However, the 5-year survival and recurrence free survival were similar in both groups (*4,86,87*). In addition, in long-term clinical practice the Consensus Committee has found that after right hemihepatectomy combined with caudate lobe resection, the remaining left liver may grow, with the liver hilum rotating towards the right. This can lead to compression of the biliary-enteric anastomosis and impaired drainage, thereby increasing the risk of cholangitis and biliary calculi in the remnant liver. Moreover, for Bismuth-Corlette type III and IV cases where extensive hepatectomy cannot be tolerated, surgical plans such as tumor resection combined with segment S4b and S5 resection or combined resection of the central liver lobes (segments S4, 5, 8, 1, 9, or segments S4, 1, 9) can be used for radical treatment and to achieve damage control.

<u>*Recommendation 14*</u>:

Individualized surgical plans should be based on the patient's condition. The goal is to achieve an R0 resection, and preserving a sufficient functional FLR is essential. Definitively excluding tumor invasion of the caudate lobe bile ducts is challenging based solely on imaging findings that show no evidence of bile duct dilation. For Bismuth type I cases without vascular invasion, tumor and extrahepatic bile duct resection with regional lymphadenectomy is recommended. For type II cases, caudate lobe resection should be added. Type III and IV hCCA necessitate hemihepatectomy, central lobectomy, or more extensive resection. [Evidence Level: 2+, Recommendation Grade: B]

9.5. Combined vascular resection and reconstruction

The liver's unique vascular anatomy, characterized by the bile duct, artery, and portal vein being encapsulated within Glisson's capsule, combined with axial spread and radial infiltration, makes vascular involvement a common feature in hCCA. Specifically, the right hepatic artery, which traverses behind the common hepatic duct and lies close to the origin of the right hepatic duct, is more susceptible to tumor invasion than the left hepatic artery.

Recent literature, consensus, and clinical guidelines agree on the clinical value of combined segmental portal vein resection and reconstruction for hCCA with portal vein involvement. The widely accepted view is that segmental portal vein resection and reconstruction do not increase postoperative complications. Instead, they improve the rate of an R0 resection and OS (*4,21,65,88*). The length of portal vein resection depends on the extent of tumor invasion, and the complexity of reconstruction is determined by its location. Therefore, a sufficient portal vein length after right liver resection allows for simple resection, repair, or anastomosis, whereas left liver resection often necessitates more complex techniques such as patching or vein grafting for reconstruction. Additionally, whether there are any variations in the bifurcation of the portal vein needs to be determined (*89*).

Combined hepatic artery resection also increases the rate of an R0 resection and benefits some previously inoperable patients but provides significantly less prognostic improvement compared to portal vein resection and reconstruction. Hepatic artery reconstruction is technically challenging, with low long-term patency rates and a high incidence of complications such as bleeding, thrombosis, and aneurysm, as well as increased mortality. These factors limit its widespread clinical acceptance (*72,90*). When imaging studies show tumor invasion of the hepatic artery, the morphological characteristics of the hepatic arterial system should be carefully analyzed preoperatively, and different surgical plans should be weighed. The key considerations are as follows: (1) whether the remaining liver can retain the blood supply from branches of the hepatic artery or phrenic artery, (2) whether high-quality arterial reconstruction can be performed in the remaining liver (including the use of the uninvolved hepatic artery on the affected side, the gastroduodenal artery, or the splenic artery), (3) if imaging suggests tumor invasion of bilateral

hepatic artery branches or the proper hepatic artery, mobilization of the remaining liver needs to be avoided and the vascular branches within the perihilar ligaments need to be protected, (4) if arterial reconstruction cannot be carried out after resection of the invaded artery, the potential for liver abscess after surgery needs to be monitored and preventive measures need to be taken as early as possible, (5) if the tumor is found to only invade the arterial sheath without penetrating the adventitia, intrasheath dissection and tumor stripping along the plane of the adventitia can be performed, and (6) the risk of intrasheath dissection lies in the potential for excessive traction, which may injure the arterial intima, leading to the formation of postoperative pseudoaneurysms and bleeding. This procedure should be performed with caution in elderly patients or those with atherosclerosis (*72*).

Recommendation 15:

Portal vein resection enables a better R0 resection with improved OS and acceptable complications. It should be considered for patients with portal vein invasion. The role of hepatic artery resection is controversial. It is associated with high morbidity and mortality and should be performed in selected patients at experienced centers. [Evidence Level: 2+, Recommendation Grade: B]

9.6. Lymph node dissection

According to Kitagawa *et al*., the most commonly involved lymph nodes in hCCA are around the common bile duct (42.7%), followed by those around the portal vein (30.9%), the hepatic artery (27.3%), and the posterior pancreaticoduodenal nodes (14.5%) (*91*). The 8th edition of the TNM staging system removed recommendations on the total number of lymph nodes for dissection and did not define the extent of lymphadenectomy for hCCA. It only recommends dissecting at least six lymph nodes to accurately assess lymph node metastasis. Regional lymph nodes are defined as those located along the hepatic hilum, cystic duct, common bile duct, hepatic artery, posterior pancreaticoduodenal region, and portal vein, while positive nodes outside these areas are classified as M1 disease (*72*). pN0 is defined as no metastasis in regional lymph nodes. Cases with negative regional nodes but fewer than six examined are still classified as pN0. pN1 is defined as 1-3 regional lymph node metastases. pN2 is defined as ≥ 4 regional lymph node metastases (*54*). The JSBS staging system specifies that lymphadenectomy for hCCA should include lymph nodes in the hepatoduodenal ligament (Station 12), around the hepatic artery (Station 8), and posterior-superior pancreatic head nodes (Station 13a), without specifying the number of nodes to dissect (*92*).

Radical resection begins with the clearance of Station 8 lymph nodes. It involves carefully exposing and suspending the common hepatic artery and then dissecting to the left, to the right, and upward. This approach facilitates the en bloc resection of the specimen. Subsequently, Station 9, 12, and 13a lymph nodes should be cleared. If no enlarged lymph nodes are found, the extent of dissection should not be expanded to stations 16 and13b.

Recommendation 16:

Standard lymphadenectomy for hCCA should include lymph nodes within the hepatoduodenal ligament (Station 12), those along the hepatic artery (Station 8), and posterior-superior pancreaticoduodenal nodes (Station 13a). Dissecting Station 9 facilitates en bloc resection. If no enlarged nodes are found, dissection should not be extended to stations 16 and 13b. [Evidence Level: 2+, Recommendation Grade: B]

9.7. Liver transplantation

The Mayo Clinic proposed a liver transplantation protocol following neoadjuvant chemoradiotherapy. Diagnosis of hCCA had to be established with brush cytology or biopsy or with CA19-9 greater than 100 ng/mL in the presence of a radiographically malignant stricture in the absence of cholangitis. In addition, the tumor had to be deemed unresectable by experienced hepatobiliary surgeons in the absence of PSC. Patients with PSC are eligible even if the tumor is resectable. The size of the tumor must be less than 3 cm. Patients with intrahepatic metastases, evidence of extrahepatic disease (including lymph nodal metastases), uncontrolled infections, prior surgery, prior radiation/chemotherapy, or percutaneous biopsy are excluded from this protocol. The protocol includes external beam radiation therapy (a dose of 45Gy in 30 fractions) with 5-fluorouracil (5-FU) administered during the first three days of radiation. Two to three weeks after external beam radiation, brachytherapy with Ir-192 (a dose of 20–30Gy) is initiated. Concurrently, a continuous infusion of 5-FU is maintained until the liver transplantation procedure. Capecitabine may be administered during the waiting period. All patients underwent staged laparotomy before liver transplantation. Preliminary results from 11 patients were published in 2000, showing promising outcomes. The final study results, published in 2005, reported a 5-year survival rate of 82% (*93-95*). Subsequently, multicenter clinical studies were initiated in line with the Mayo criteria.

Numerous studies have demonstrated that neoadjuvant chemoradiotherapy followed by liver transplantation can offer long-term survival for carefully selected patients with unresectable hCCA, and particularly those with PSC-related hCCA (*96,97*). For patients with resectable hCCA, whether they can benefit from liver transplantation remains a question. A study by Croome *et al*. suggested that radical surgical resection remains the recommended approach for resectable hCCA patients,

as there is currently no high-level evidence supporting the superiority of liver transplantation over surgical resection (*98*). Additionally, the scarcity of donor organs and the complexity of liver transplantation techniques must be considered. Currently, radical resection surgery remains the standard treatment for hCCA according to major guidelines. Most guidelines advise participation in clinical trials or, in strictly selected patients with chronic liver diseases such as PSC, consideration of liver transplantation (*17,19,39*). As the "ultimate weapon" for treating end-stage liver disease, liver transplantation can not only achieve an R0 resection of the tumor but also restore liver function in carefully selected hCCA patients with PSC.

Recommendation 17:

Due to the scarcity of donor organs and the lack of PSC background in most domestic patients, a radical cure can be achieved in the majority of patients meeting the Mayo transplant criteria through surgical resection. Liver transplantation should only be considered for those who are no longer able to undergo surgery and who exhibit no lymph node or distant metastasis. [Evidence Level: 2+, Recommendation Grade: B]

9.8. Minimally invasive techniques

Laparoscopic techniques were initially used in hCCA for intraoperative exploration and tumor staging (*99, 100*). Laparoscopic exploration for hCCA should begin with a thorough examination of the liver, peritoneum, and lymph nodes outside the hepatic hilum to determine the feasibility of regional resection. If Station 16 lymph nodes are enlarged, intraoperative rapid pathology should be performed, and positive biopsy results should lead to abandoning radical surgery in favor of systemic therapy.

Laparoscopic techniques have gradually been used for radical hCCA surgery. A 2020 systematic review that examined the state of laparoscopic radical surgery for hCCA in China included 13 studies and 189 patients. Results indicated that the average operating time was 354 minutes, the average intraoperative blood loss was 324 milliliters, the rate of an R0 resection was 95.2%, the average number of lymph nodes dissected was 9.5, the conversion rate to open surgery was 2.6%, the complication rate was 21.2%, and the 1-year OS rate for patients was 84.5% (*101*). A 2023 multicenter real-world study by Chinese researchers compared the efficacy of laparoscopic and open surgery for hCCA and revealed equivalent short-term and long-term outcomes (*102*). According to the expert consensus, laparoscopic radical resection of hCCA is indicated for patients with Bismuth-Corlette type I and II hCCA, as well as selected cases of Bismuth-Corlette type III and IV hCCA without vascular invasion (*103*). Vascular invasion in the hepatic hilum significantly increases the technical difficulty of laparoscopic surgery due to the limited operative space and complexity of the procedure. Although laparoscopic hepatic artery resection and reconstruction has been reported, the procedure is technically challenging, so it is not recommended routinely (*104*). Portal vein invasion is relatively easier to resect and reconstruct, with some experienced hepatobiliary surgical centers reporting successful cases. Robotic surgery is an emerging minimally invasive approach for radical hCCA treatment, but current studies, both domestic and international, are mostly case reports lacking an analysis of large samples.

Due to the anatomical complexity and biological characteristics of hCCA, radical surgery typically involves combined liver segment and caudate lobe resection, biliary-enteric anastomosis, regional lymph node dissection, and vascular resection and reconstruction. Both laparoscopic and robotic surgeries present significant technical challenges and require advanced surgical skills. Currently, most of the relevant studies are limited to case reports and small-sample studies (*105,106*). Minimally invasive laparoscopic surgery is a promising field, but further RCTs are needed to prove its advantages over traditional open surgery and to develop standardized surgical procedures. Therefore, laparoscopic and robotic radical resection for hCCA should be performed at experienced hepatobiliary surgery centers with extensive expertise in minimally invasive procedures, and only after careful selection of suitable hCCA patients.

Recommendation 18:

For patients with hCCA who are preparing to undergo surgery, undergoing laparoscopic exploration first is recommended to determine the feasibility of radical resection. Laparoscopic and robotic radical resection of hCCA is recommended at hepatobiliary surgery centers with extensive experience in minimally invasive surgery and for carefully selected hCCA cases. [Evidence Level: 2++, Recommendation Grade: A]

10. Local treatment

10.1. Biliary drainage

The majority of hCCA cases also involve malignant obstructive jaundice. In recent years, the benefits of PBD have been increasingly recognized. For palliative care patients, biliary drainage not only allows them to benefit from systemic treatment but also aids in the prevention and treatment of cholangitis, thereby relieving symptoms. The most frequently used techniques are PTBD and ERCP.

There remains controversy over whether PTBD or ERCP should be the preferred method of biliary drainage (*107*). Advantages of PTBD include precise catheter placement to maximize bile drainage, quicker achievement of a satisfactory reduction in bilirubin compared to ERCP, and a lower risk of biliary infection. However, PTBD is invasive and may increase the risk of

tumor seeding and dissemination (*108,109*). Prolonged PTBD exceeding 60 days is an independent risk factor for tumor dissemination and reduced postoperative survival (*110*). ERCP, in contrast, is less invasive but more technically challenging, with a potential for higher rates of biliary infection. Chinese researchers tend to favor PTBD, whereas Japanese researchers lean towards ERCP (*64,65*). The British Society of Gastroenterology guidelines for cholangiocarcinoma recommend selecting methods of drainage based on specific conditions. For instance, ERCP is preferred for patients requiring biopsy or brush cytology, whereas PTBD is more suitable for complex hCCA cases, such as Bismuth type IV, where ERCP has a high failure rate (*39*).

Recently, EUS-guided biliary drainage (EUS-BD) has garnered increasing attention in clinical practice. Given its technical complexity, EUS-BD requires highly skilled operators, and further research is needed to confirm its clinical efficacy and long-term prognosis. EUS-BD may be used for patients where ERCP fails. EUS-BD combined with hepatogastrostomy can be a valuable option for patients with an unresectable malignant hilar bile duct obstruction and left hepatic duct dilatation, when ERCP and/or PTBD are inadequate (*111*). The choice of optimal biliary drainage for hCCA patients should follow an individualized approach, taking into account the anatomical location of the obstruction, the goals of drainage, the availability of equipment, the operator's skill level, and the patient's status.

10.2. Endoscopic biliary stent placement

The primary debates regarding stent placement for malignant hilar biliary obstruction concern the type of stent (plastic *vs.* metal) and the extent of drainage (unilateral *vs.* bilateral). A plastic stent (PS) is easy to replace and does not interfere with other therapeutic efforts, such as local ablation or surgery. Thus, a PS is recommended for PBD. However, due to its smaller diameter, a PS has a higher failure rate and requires frequent replacement, potentially reducing quality of life and increasing costs. A self-expandable metal stent (SEMS), with its larger diameter, provides longer patency and is easier to pass through stenotic segments (*112*). Studies comparing SEMSes and PSes have indicated that SEMSes result in higher technical and clinical success rates, less need for re-intervention, and greater cost-effectiveness due to extended stent patency (*113,114*). Therefore, SEMSes are mainly used for palliative biliary drainage. For hCCA with a predicted survival of <3 months, a PS or an uncovered SEMS is recommended. For those with a predicted survival > 3 months, an SEMS is preferred over a PS (*27*). If the future treatment strategy is uncertain, SEMS insertion should be avoided (*115*).

There is no consensus yet regarding unilateral versus bilateral stents. Increasingly, experts believe that the goal of stent placement for hilar strictures is to drain >50% of the liver volume. When a single stent cannot achieve this, bilateral drainage should be considered for better clinical outcomes (*45*).

Recommendation 19:

For PBD, use of a PS is recommended. An SEMS is primarily for palliative biliary drainage. For hCCA with a predicted survival of <3 months, a PS or an uncovered SEMS is recommended. For hCCA with a predicted survival of >3 months, an SEMS is preferred over a PS. If the treatment strategy remains uncertain, SEMS insertion should be avoided. For patients with hilar stricture, the goal of stent placement should be to drain >50% of the liver volume. [Evidence Level: 2+, Recommendation Grade: B]

10.3. Intraluminal therapy

Most patients with unresectable hCCA experience malignant obstructive jaundice requiring biliary drainage. Biliary stenting improves quality of life, and intraluminal therapies can be used concurrently with drainage. Research has indicated that combining chemotherapy with intraluminal therapy improves survival and quality of life in unresectable hCCA by controlling local tumor growth and extending stent patency (*116-118*). Intraluminal therapeutic techniques include radiofrequency ablation (RFA), photodynamic therapy (PDT), and intraluminal brachytherapy (ILBT).

Intraluminal RFA:RFA uses high-frequency electric currents to generate heat, causing cellular dehydration, coagulation, and necrosis, ultimately killing tumor cells (*112*). RFA is primarily used for palliative treatment of unresectable hCCA, improving survival and quality of life compared to stenting alone (*119*). Two small-scale studies indicated that combining RFA with stents extended patient survival and stent patency compared to stenting alone, without increasing adverse event rates (*120,121*). Moreover, RFA combined with systemic chemotherapy improved efficacy in treating unresectable hCCA, further prolonging survival (*122,123*). For patients with malignant biliary obstruction, stent occlusion and tumor regrowth are major concerns. Intraluminal RFA can help unclog stents blocked by tumor growth, and combining RFA with stents may enhance stent patency rates (*119,124*).

PDT: PDT uses photosensitizers that selectively accumulate in proliferating tumor cells and that are cytotoxic when subjected to specific laser wavelengths. PDT is minimally invasive, precise, and repeatable, making it suitable for palliative treatment of unresectable hCCA (*125*). A 2022 meta-analysis indicated that PDT combined with biliary stents improved survival in patients with unresectable hCCA without increasing adverse events (*126*). PDT also extended stent patency (*127*). Studies have shown that PDT and chemotherapy

have a synergistic effect; they are often administered sequentially, with PDT preceding chemotherapy (*117,118,128*). PDT can be repeated at approximately three-month intervals (*129*). Some studies are currently exploring the potential of PDT as a neoadjuvant therapy for hCCA, with ongoing clinical trials such as NCT04824742 investigating its efficacy and safety. Due to its minimally invasive and precise nature, PDT holds significant promise as a palliative treatment option for hCCA.

ILBT: ILBT offers the advantages of a small radiation radius, long half-life, sustained tumor cell killing, and minimal damage to adjacent tissues (*130*). A meta-analysis of 981 patients with malignant biliary obstruction found that ILBT combined with stenting reduced the risk of stent obstruction, improved survival, and did not increase complications compared to stenting alone (*131*). However, the clinical use of ILBT is limited due to its complexity, challenges managing radioactive materials, and potential late complications such as duodenal stricture and gastrointestinal bleeding (*130*). Recent advances include biliary stents combined with iodine-125 seeds. A study has indicated that such combinations extend stent patency and improve survival (*132*). A small-scale retrospective study conducted at the Sun Yat-sen University Cancer Center reported encouraging outcomes for patients treated with stents and iodine-125 seeds, followed by systemic therapies such as lenvatinib and PD-1 inhibitors. Results indicated a median survival of 6.1 months, with significant bilirubin reduction within four weeks. ILBT remains a palliative option for patients with advanced disease, with potential for further clinical exploration and research.

Recommendation 20:

Intraluminal therapies (RFA, PDT, and ILBT) currently lack high-quality clinical evidence. Therefore, they are not recommended as standard first-line palliative treatments for hCCA. Discussions of MDT should carefully evaluate potential benefits and risks before administering these therapies. [Evidence Level: 2-, Recommendation Grade: 0]

10.4. Radiotherapy

Neoadjuvant radiotherapy: The clinical value of neoadjuvant radiotherapy for hCCA remains under evaluation, and participation in clinical trials is encouraged. Small-scale studies suggest that preoperative radiotherapy may increase resectability, reduce recurrence, and potentially improve survival rates (*133,134*). The Mayo Clinic's neoadjuvant chemoradiotherapy protocol serves as a bridge for liver transplantation. This protocol includes external beam radiation therapy (45Gy/30 fractions) followed by brachytherapy with iridium-192 (20-30Gy) administered 2-3 weeks later (*95*).

Adjuvant radiotherapy: The data supporting adjuvant radiotherapy or chemoradiotherapy are limited and mostly come from retrospective studies. Postoperative recurrence rates for hCCA are high (60-70%), indicating that surgery alone provides limited improvement in prognosis (*135*). SWOG S0809, a phase II single-arm trial, enrolled 79 patients with extrahepatic cholangiocarcinoma and gallbladder cancer (38 with hCCA) who underwent curative resection. Eligible patients (T2-T4, N1, or positive margins) received four cycles of gemcitabine-capecitabine followed by chemoradiotherapy (45Gy for regional lymph nodes; 54-59.4Gy for the tumor bed) with capecitabine as a sensitizer. The study's primary endpoint (2-year survival > 45%) was achieved, with a 2-year survival rate of 65% and median overall survival (mOS) of 35 months (*136*). Further analysis indicated that patients with nodal involvement (N1) had a 2-year disease-free survival (DFS) rate of 49.8%, better than the historical control of 29.7%. However, high rates of distant failure (42.2%) persisted among these patients (*136,137*). A meta-analysis of 21 retrospective studies, encompassing over 1,400 patients with extrahepatic cholangiocarcinoma and gallbladder cancer, demonstrated that adjuvant radiotherapy improved 5-year OS, and especially in patients with nodal positivity or an R1 resection. Local recurrence rates were reduced, although distant metastasis rates were unchanged (*138*). Another meta-analysis included 21 studies with 6,712 patients with cholangiocarcinoma and gallbladder cancer. Results indicated that adjuvant therapy provided the greatest benefit in patients with lymph node positivity (OR = 0.49, $p = 0.004$) and an R1 resection (OR = 0.36, $p = 0.002$) (*139*). ASCO, ESMO, NCCN, and CSCO guidelines all recommend adjuvant radiotherapy for R1-resected hCCA (*17,19,62,140*). Patients with an R0 resection and nodal involvement may also benefit from adjuvant radiotherapy, which is a level II recommendation in the CSCO guidelines (*62*). The management of patients with an R2 resection is the same as that for those with unresectable hCCA. Currently, a phase III prospective randomized trial is ongoing (NCT02798510), and its results are highly anticipated.

Palliative radiotherapy: For unresectable locally advanced hCCA, clinical trial participation is encouraged. Small-sample retrospective studies suggest that chemoradiotherapy improves survival and local control rates compared to chemotherapy alone in patients with good performance status. A study of 2,996 patients with unresectable extrahepatic cholangiocarcinoma by the National Cancer Database in the United States found that, compared to the group receiving chemotherapy alone, the mOS of patients in the chemoradiotherapy group was extended from 12.6 months to 14.5 months ($p < 0.001$) (*141*). The optimal radiation dose remains uncertain, with standard recommendations around 45-50 Gy within five weeks. An increased dose may improve local control but is limited by the proximity of the

hCCA to radiation-sensitive organs like the duodenum (*64*). Several small-scale studies have indicated that metal stent placement combined with palliative external radiotherapy and/or brachytherapy may improve local tumor control, extend stent patency, and prolong survival (*142,143*). In cases of distant metastases, and particularly those involving bone or brain, palliative radiotherapy may be considered to relieve symptoms.

Recommendation 21:

Neoadjuvant chemoradiotherapy plays a pivotal role in the management of patients awaiting liver transplantation. For resectable hCCA, however, the current evidence base is limited by the absence of randomized phase III trials. Thus, eligible patients are advised to participate in clinical trials. For unresectable locally advanced hCCA, chemoradiotherapy may be considered for patients with good performance status. [Evidence Level: 2++, Recommendation Grade: A]

Recommendation 22:

Postoperative recurrence rates of 60-70% highlight the limited benefit of surgery alone. Patients with R1-resected and R0-resected node-positive hCCA should receive adjuvant chemoradiotherapy. Management of R2-resected hCCA should align with that of unresectable hCCA. [Evidence Level: 2++, Recommendation Grade: A]

11. Systemic treatment

11.1. Adjuvant chemotherapy

The BILCAP phase III multicenter RCT in the UK included 447 patients who underwent radical surgery for cholangiocarcinoma and gallbladder cancer. In the intention-to-treat analysis, the mOS was 51.1 months in the capecitabine group and 36.4 months in the observation group, so there were no significant differences in the mOS ($p = 0.097$). In the prespecified per-protocol analysis, however, the mOS was 53 months for the capecitabine group compared to 36 months for the observation group, so the mOS differed significantly ($p = 0.028$) (*144,145*). Despite limitations in the BILCAP study's results, international guidelines recommend adjuvant capecitabine treatment for six months following radical resection of hCCA as the current standard therapy (*17,19,140*).

The use of adjuvant therapy has been further supported by the Japanese JCOG1202: ASCOT phase III RCT trial, which demonstrated that adjuvant therapy with S1 (tegafur-gimeracil-oteracil, an orally acting fluoropyrimidine) prolonged OS compared to surgery alone. The 3-year OS rates for the S1 group and the observation group were 77.1% and 67.6% respectively ($p = 0.008$) (*146*). Therefore, S1 can also be considered for adjuvant chemotherapy after hCCA surgery. The Asian BCAT trial and the French PRODIGE 12 randomized trial failed to respectively demonstrate that the gemcitabine and GEMOX (gemcitabine-oxaliplatin) regimens improved recurrence-free survival and OS compared to the observation group (*147,148*). The prospective, randomized phase II STAMP study in South Korea enrolled patients with extrahepatic cholangiocarcinoma and positive lymph nodes. Adjuvant therapy with the GC (gemcitabine-cisplatin) regimen was compared to capecitabine. Results indicated that there was no significant improvement in the 2-year DFS rate and the 2-year OS rate (*149*). Other adjuvant chemotherapy regimens, primarily based on gemcitabine or 5-FU, include the GC regimen, gemcitabine-capecitabine, capecitabine-oxaliplatin, 5-FU-oxaliplatin, and 5-FU monotherapy. These primarily come from small-sample or retrospective studies.

11.2. Neoadjuvant chemotherapy

Neoadjuvant chemoradiotherapy plays a pivotal role for hCCA patients scheduled for liver transplantation. However, there is currently a lack of randomized controlled phase III clinical trials to prove the benefits of a neoadjuvant treatment strategy in routine surgical resection. Participation of eligible patients in clinical trials is recommended.

11.3. First-line treatment for unresectable or advanced hCCA

Two-drug combination chemotherapy regimens: The ABC-02 phase III RCT demonstrated that the gemcitabine-cisplatin doublet significantly extended OS in patients with advanced cholangiocarcinoma from 8.1 months (gemcitabine monotherapy) to 11.7 months ($p < 0.001$) (*150*). This established gemcitabine-cisplatin as the first-line treatment for advanced hCCA. The phase III JCOG1113/FUGA-BT non-inferiority study indicated that gemcitabine-S1 achieved an OS of 15.1 months, comparable to gemcitabine-cisplatin (13.4 months), making it an alternative first-line therapy for advanced cholangiocarcinoma (*151*).

Immunotherapy-based chemotherapy regimens: The TOPAZ-1 phase III RCT indicated that durvalumab combined with gemcitabine-cisplatin as first-line therapy for advanced cholangiocarcinoma improved mOS from 11.3 months (gemcitabine-cisplatin alone) to 12.9 months, and median progression-free survival (mPFS) from 5.7 months to 7.2 months (*152*). The KEYNOTE-966 phase III RCT found that pembrolizumab combined with gemcitabine-cisplatin as first-line therapy for advanced cholangiocarcinoma increased mOS from 10.9 months (chemotherapy alone) to 12.7 months, with no significant increase in toxicity (*153*). Therefore, durvalumab or pembrolizumab combined with gemcitabine-cisplatin is recommended as a first-line therapy for advanced cholangiocarcinoma.

Triple-drug chemotherapy regimens: The KHBO1401 phase III RCT in Japan demonstrated that the gemcitabine-cisplatin-S1 combination achieved an OS of 13.5 months, superior to 12.6 months for gemcitabine-cisplatin alone (p = 0.046) (*154*). Thus, for hCCA patients with a good performance status, the gemcitabine-cisplatin-S1 triple regimen can also be considered a first-line therapy.

11.4. Second-line Treatment for Advanced hCCA

Chemotherapy: The ABC-06 phase III study enrolled patients with advanced cholangiocarcinoma that progressed after first-line gemcitabine-cisplatin treatment. Results indicated that the mFOLFOX group had a survival advantage (OS: 6.2 months *vs.* 5.3 months, p = 0.031) over active symptom control (ASC) (*155*). Thus, mFOLFOX is recommended as a second-line treatment regimen for advanced cholangiocarcinoma. The FOLFIRI and irinotecan-capecitabine (XELIRI) regimens have demonstrated favorable survival benefits and tolerability in the second-line treatment of advanced cholangiocarcinoma, making them viable options (*156,157*). The phase IIb NIFTY study revealed that liposomal irinotecan combined with fluorouracil and leucovorin achieved a progression-free survival (PFS) of 7.1 months, compared to 1.4 months for fluorouracil and leucovorin alone in advanced cholangiocarcinoma (*158*). Chemotherapy for hCCA patients primarily involves gemcitabine- or fluorouracil-based regimens. Second-line chemotherapy options may include other unused first-line recommended regimens, according to the individual patient's treatment history, as well as institutional experience.

Targeted therapy and immunotherapy: Patients with advanced or progressive disease should undergo comprehensive genetic testing, including that for HER2 overexpression or amplification, IDH1/2 mutations, FGFR2 fusions, BRAF V600E mutations, NTRK fusions, RET fusions, and microsatellite instability, to guide targeted therapy and immunotherapy (*17,159*). This approach enables personalized treatment strategies based on the molecular profile of the tumor, potentially improving therapeutic outcomes. Ivosidenib for IDH1 mutations and pemigatinib for FGFR2 fusions have been approved for second-line treatment of advanced cholangiocarcinoma. However, IDH mutations and FGFR fusions are rare in hCCA patients. HER2 is a noteworthy target in hCCA patients. The MyPathway study enrolled 39 patients with HER2-positive cholangiocarcinoma, and trastuzumab-pertuzumab achieved an objective response rate (ORR) of 23%, mPFS of 4 months, and mOS of 10.9 months (*160*). The HERB study, a multicenter, single-arm phase II trial, included 30 patients with HER2-positive or low-expression cholangiocarcinoma refractory to gemcitabine, and trastuzumab deruxtecan achieved an ORR of 36.4% and a disease control rate (DCR) of 81.8% (*161,162*). Other therapeutic targets include BRAF V600E mutations, NTRK fusions, and RET fusions. Dabrafenib-trametinib achieved an ORR of 51%, mPFS of 9 months, and mOS of 14 months in patients with advanced cholangiocarcinoma with BRAF V600E mutations (*163*). Pembrolizumab immunotherapy can be considered for patients with MSI-H tumors (*164*). Entrectinib and larotrectinib, inhibitors targeting NTRK fusions, have been approved for treating advanced solid tumors with NTRK fusion positivity. Pralsetinib or selpercatinib may be considered for treatment of RET fusion-positive patients (*17,62*).

There are no precision targets in the majority of hCCA patients. Multi-target drugs such as lenvatinib, anlotinib, and sulfatinib are used in clinical practice. However, high-level clinical evidence for these drugs still needs to be compiled. A single-arm study involving 41 patients with advanced cholangiocarcinoma who underwent at least one systemic therapy reported an ORR of 12%, mPFS of 3.8 months, and mOS of 11.4 months with lenvatinib monotherapy until disease progression (*165*). A real-world study involving 57 patients with advanced cholangiocarcinoma (9 with extrahepatic cholangiocarcinoma) treated with lenvatinib combined with a PD-1/PD-L1 inhibitor and the GEMOX regimen indicated an mPFS of 9.27 months and mOS of 13.4 months (*166*). A phase Ib study of 66 patients with advanced cholangiocarcinoma who failed to respond to first-line treatment reported an ORR of 21.21%, DCR of 72.73%, and mOS and mPFS of 15.77 months and 6.24 months, respectively, using anlotinib combined with benmelstobart (*167*). A phase II study involving 20 patients with advanced cholangiocarcinoma that progressed after first-line chemotherapy indicated an ORR of 30%, DCR of 90%, and mOS and mPFS of 12.3 months and 6.5 months, respectively, with anlotinib and sintilimab (*168*). Another phase II single-arm study of 39 patients with advanced cholangiocarcinoma undergoing second-line therapy reported a 16-week PFS rate of 46.33% with surufatinib (*169*).

Recommendation 23:

(1) After radical resection, capecitabine adjuvant chemotherapy for 6 months is recommended. [Evidence level: 1-, Recommendation grade: A]

(2) First-line treatment: The GC regimen, GS (gemcitabine-S1) regimen, GC combined with durvalumab, or GC combined with pembrolizumab is recommended. [Evidence level: 2++, Recommendation grade: A]. For patients with a good performance status, the three-drug combination regimen (GC plus S1) is recommended as first-line treatment. [Evidence level: 2++, Recommendation grade: A]

(3) Second-line treatment: The FOLFOX regimen is recommended. [Evidence level: 2++, Recommendation grade: A]. Irinotecan-based combination regimens,

such as FOLFIRI or XELIRI, may also be considered. [Evidence level: 2++, Recommendation grade: A]

(4) Molecular analysis is recommended to guide second-line treatment: ① For IDH1 mutations, ivosidenib is recommended; ② For patients positive for FGFR2 fusions, pemigatinib is recommended; ③ For BRAF V600E mutations, the combination of dabrafenib and trametinib is recommended; ④ For patients positive for NTRK fusions, entrectinib or larotrectinib is recommended; ⑤ For HER2 amplification, trastuzumab plus pertuzumab or trastuzumab deruxtecan is recommended; ⑥ For those with MSI-H, pembrolizumab immunotherapy is recommended. [Evidence level: 2+, Recommendation grade: B]

12. Conclusion

hCCA is characterized by high malignancy and presents significant challenges in surgical resection, which contribute to its dismal prognosis. Proactive screening and early diagnosis are crucial to identifying hCCA and improving early detection rates. Selecting appropriate treatment strategies and surgical techniques ensures complete tumor resection while preserving residual liver function and minimizing postoperative complications. Moreover, multidisciplinary comprehensive care, along with standardized local and systemic treatments, allows for full-cycle management of hCCA patients. This holistic approach is pivotal to improving treatment outcomes and overall prognosis.

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