

Chinese national clinical practice guideline on diagnosis and treatment of biliary tract cancers

Xu'an Wang¹, Yongrui Bai², Ningli Chai³, Yexiong Li⁴, Enqiang Linghu³, Liwei Wang⁵, Yingbin Liu¹; Society of Hepato-pancreato-biliary Surgery of Chinese Research Hospital Association, Society of Digestive Endoscopy of the Chinese Medical Association, Chinese Medical Journal Clinical Practice Guideline Collaborative

¹Department of Biliary and Pancreatic Surgery, Renji Hospital, Shanghai Jiao Tong University School of Medicine; State Key Laboratory of Systems Medicine for Cancers, Shanghai Cancer Institute; Shanghai Key Laboratory for Cancer Systems Regulation and Clinical Translation, Shanghai 200127, China;

²Department of Radiation Oncology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China;

³Department of Gastroenterology and Hepatology, the First Medical Center, Chinese People's Liberation Army General Hospital, Beijing 100853, China;

⁴State Key Laboratory of Molecular Oncology and Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing 100853, China;

⁵State Key Laboratory of Oncogenes and Related Genes, Shanghai Cancer Institute; Department of Oncology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China.

Abstract

Background: Biliary tract carcinoma (BTC) is relatively rare and comprises a spectrum of invasive tumors arising from the biliary tree. The prognosis is extremely poor. The incidence of BTC is relatively high in Asian countries, and a high number of cases are diagnosed annually in China owing to the large population. Therefore, it is necessary to clarify the epidemiology and high-risk factors for BTC in China. The signs associated with BTC are complex, often require collaborative treatment from surgeons, endoscopists, oncologists, and radiation therapists. Thus, it is necessary to develop a comprehensive Chinese guideline for BTC.

Methods: This clinical practice guideline (CPG) was developed following the process recommended by the World Health Organization. The Grading of Recommendations Assessment, Development, and Evaluation approach was used to assess the certainty of evidence and make recommendations. The full CPG report was reviewed by external guideline methodologists and clinicians with no direct involvement in the development of this CPG. Two guideline reporting checklists have been adhered to: Appraisal of Guidelines for Research and Evaluation (AGREE) and Reporting Items for practice Guidelines in Healthcare (RIGHT).

Results: The guideline development group, which comprised 85 multidisciplinary clinical experts across China. After a controversies conference, 17 clinical questions concerning the prevention, diagnosis, and treatment of BTC were proposed. Additionally, detailed descriptions of the surgical principles, perioperative management, chemotherapy, immunotherapy, targeted therapy, radiotherapy, and endoscopic management were proposed.

Conclusions: The guideline development group created a comprehensive Chinese guideline for the diagnosis and treatment of BTC, covering various aspects of epidemiology, diagnosis, and treatment. The 17 clinical questions have important reference value for the management of BTC.

Keywords: Biliary tract carcinoma; Etiology; Diagnosis; Treatment; Surgery

Introduction

Biliary tract carcinoma (BTC) comprises gallbladder cancer (GBC), intrahepatic cholangiocarcinoma (iCCA), and extrahepatic cholangiocarcinoma (eCCA), including perihilar cholangiocarcinoma (pCCA) and distal cholangiocarcinoma (dCCA). The vast majority of BTCs are adenocarcinomas, with strong invasiveness. BTCs are detected most often in the late stage and have a very poor

Correspondence to: Yingbin Liu, Department of Biliary and Pancreatic Surgery, Renji Hospital, Shanghai Jiao Tong University School of Medicine; State Key Laboratory of Systems Medicine for Cancers, Shanghai Cancer Institute; Shanghai Key Laboratory for Cancer Systems Regulation and Clinical Translation, Shanghai 200127, China

E-Mail: laoniulyb@shsmu.edu.cn;

Liwei Wang, State Key Laboratory of Oncogenes and Related Genes, Shanghai Cancer Institute, Department of Oncology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China

E-Mail: liweiwang@shsmu.edu.cn;

Enqiang Linghu, Department of Gastroenterology and Hepatology, the First Medical Center, Chinese People's Liberation Army General Hospital, Beijing 100853, China

E-Mail: linghuenqiang@vip.sina.com;

Yexiong Li, State Key Laboratory of Molecular Oncology and Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing 100853, China

E-Mail: yexiong12@163.com

Copyright © 2024 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2024;137(19)

Received: 25-02-2024; Online: 04-09-2024 Edited by: Yuanyuan Ji

Access this article online

Quick Response Code:



Website:

www.cmj.org

DOI:

10.1097/CM9.0000000000003258

prognosis, with a 5-year survival rate of <5%. Currently, the global incidence rate of BTC is increasing, especially in Asian countries.^[1]

Audience for the guideline

This clinical practice guideline (CPG) is intended for use by doctors and nursing staff engaged in BTC surgery, oncology, gastroenterology, endoscopy, radiotherapy, interventional therapy, pathology, nutrition, and related fields. The CPG is a reference for pharmaceutical companies engaged in the research of targeted drugs, immunotherapy drugs, chemotherapy drugs, and related drugs for BTC, as well as for patients with biliary tumors or high-risk factors for BTC.

Contents and update plan

The contents comprise four parts: overview, diagnosis, treatment (surgery, perioperative management, internal medicine treatment, and radiotherapy), and follow-up, with a total of 17 recommendations. This guide is intended to be updated in the year 2026.

Methods

This CPG was developed following the process recommended by the World Health Organization (WHO).^[2] The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess the certainty of the evidence and make recommendations. This CPG has been registered on the Guidelines International Network website (<https://guidelines.ebmportal.com/chinese-national-clinical-practice-guideline-diagnosis-and-treatment-biliary-tract-cancers>).

The guideline development group, which comprised 85 multidisciplinary experts on surgery, gastroenterology, oncology, radiotherapy, and methodology across China, identified 52 important clinical questions through discussion. After a controversies conference, 17 clinical questions were proposed by anonymous voting, and converted into research questions using the Population, Intervention, Comparison, and Outcomes (PICO) format in preparation for systematic reviews. Then, the evidence review team searched PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure, China Biomedical Database, and WanFang databases in 2023, with no limits regarding date or language. After reviewing the evidence for each PICO question, consensus was reached through open discussion and voting, where 70% was adopted as the threshold to pass a recommendation. The strengths of the recommendations in this CPG are categorized as strong, weak, and conditional. The factors that promote a strong recommendation comprise high certainty of evidence, similarity in stakeholders' values and preferences, cost effectiveness, and sharp contrast between benefit and harm.^[3]

The full CPG report was reviewed by external experts with no direct involvement in its development. Their feedback was collected and incorporated, as appropriate.

Two guideline reporting checklists have been adhered to: Appraisal of Guidelines, Research and Evaluation (AGREE) and Reporting Items for practice Guidelines in Healthcare (RIGHT).^[4–8]

Overview

Anatomic classification

BTC refers to a malignant tumor that originates in the epithelial cells of the bile ducts.^[9] The biliary system, anatomically categorized as intrahepatic bile ducts, extrahepatic bile ducts, and the gallbladder, can correspondingly give rise to different types of cholangiocarcinoma on the basis of anatomical considerations.^[10]

iCCA: Malignancy in the epithelial cells of bile duct branches at the second level or higher. Three growth patterns have been described: (i) Mass-forming, the most common growth pattern; (ii) Periductal-infiltrating, which infiltrates along the lumen wall; and (iii) Intraductal-growing, the least common subtype.

pCCA: pCCA arises in the epithelial tissues of the left and right hepatic ducts, the confluence area, and the common hepatic duct. This type is most prone to invading the blood vessels of the hepatic hilum. The extent of pCCA may be described by the Bismuth–Corlette classification: (i) Type I: below the confluence of the left and right hepatic ducts; (ii) Type II: reaching the confluence but not involving the left or right hepatic ducts; (iii) Type III: occluding the common hepatic duct and either the right (IIIa) or left (IIIb) hepatic duct; and (iv) Type IV: multicentric or bilateral intrahepatic segmental involvement, or involving the confluence and both the right and left hepatic ducts.

GBC: Malignant tumors originating in the epithelial cells of the gallbladder, including various types, such as gallbladder duct carcinoma, gallbladder neck carcinoma, gallbladder body carcinoma, and gallbladder fundus carcinoma.

dCCA: dCCA arises in the epithelial cells of the common bile duct beyond the opening of the gallbladder duct and above the ampulla.

These cholangiocarcinomas can exhibit various histopathological types, namely cholangiocellular carcinoma, squamous cell carcinoma, adenosquamous carcinoma, and undifferentiated carcinoma.

Etiology and risk factors

The varying regional incidence of cholangiocarcinoma reflects different underlying risk factors. Risk factors share chronic inflammation of the biliary epithelium as a key feature.^[11] Generally, the risk factors for BTC include primary sclerosing cholangitis, Caroli's disease, hepatolithiasis, and liver fluke infections. Other risk factors are cirrhosis, hepatitis B and hepatitis C infections, obesity-associated liver disease, and diabetes. Underlying hepatic inflammation, fibrosis, or cirrhosis are risk factors

for iCCA.^[12] A previous meta-analysis showed that stones, cirrhosis, and hepatitis B and C infections are the strongest risk factors for both iCCA and eCCA.^[13] However, it is important to recognize that most patients with cholangiocarcinoma have no identifiable risk factors. Although in high-income countries, cholangiocarcinoma is associated with chronic inflammation of the biliary tree and hepatic parenchyma, in Thailand, chronic infection with liver flukes is the driving risk factor. Endemic liver fluke infection (*Opisthorchis viverrini*) is associated with eating raw or undercooked fish for ≥ 20 years. Endemic areas for *Clonorchis sinensis* are China, Korea, and Vietnam.^[14] Recently, diabetes, obesity, and the use of hormonal contraceptives have been associated with an 81%, 62%, and 62% increased risk of developing iCCA, respectively.^[12,15] Screening for CCA in these newly-defined at-risk groups has not yet been established.^[16]

The risk of GBC increases with age, and GBC is more common in women than in men.^[17] Predisposing conditions that cause cholecystitis are associated with a high incidence of GBC. Gallstones are the strongest risk factor;^[18,19] others include porcelain gallbladder, gallbladder polyps, primary sclerosing cholangitis,^[20] chronic *Salmonella typhi* or *Helicobacter bilis* infection,^[21] congenital biliary tree malformations (e.g., choledochal cysts, congenital biliary dilatation, and anomalous pancreaticobiliary ductal junction), and obesity.^[22,23]

Incidence and epidemiology

BTCs account for <1% of all human cancers and approximately 2.2% of all digestive tumors.^[24] BTCs refer to a spectrum of invasive tumors, including gallbladder carcinoma or cholangiocarcinoma, arising from the biliary tree. Cholangiocarcinoma is the second most common primary liver cancer after hepatocellular carcinoma, accounting for 10%–15% of all primary liver cancers.^[25] The incidence of cholangiocarcinoma is low in high-income countries (from 0.35 cases per 100,000 to 2 per 100,000 annually); however, in the endemic regions of Thailand, Korea, and China, the incidence is up to 40 times higher.^[11,26]

The new International Classification of Diseases, version 11 classification includes specific codes for iCCA, pCCA, dCCA, and GBC, aiming to harmonize future epidemiological data.^[27] iCCAs occur less commonly in east Asia, where fluke-related cancers increase the relative proportion of pCCA.^[28] Although overall CCA rates in Asia have remained static, the incidence of iCCA has increased steadily in most Western countries, while the incidence of d/pCCA has remained stable or decreased.^[11,29,30]

Regarding GBC, an estimated 115,949 new cases and 84,695 deaths were reported worldwide in 2020, with substantial variation by sex and geographical region.^[24] The highest rates are observed in women from southern Chile, followed by northern India, Poland, southern Pakistan, and Japan. The incidence is relatively uniform or decreasing in high-income countries,^[31] likely because of the increase in routine cholecystectomy.

Diagnosis

Clinical manifestations

Except for pCCA and dCCA, which can manifest with jaundice, iCCA, GBC, and other BTCs generally lack noticeable symptoms in the early to middle stages.^[32–37]

GBC: GBC typically lacks specific symptoms in the early stages, often presenting as subtle discomfort or vague pain in the upper abdomen. As the tumor progresses, patients may experience progressive worsening of right upper abdominal pain, accompanied by loss of appetite and weight loss. If the tumor affects the common bile duct, obstructive jaundice could occur.

iCCA: This cancer usually present with nonspecific symptoms. As the disease progresses, abdominal discomfort, pain, fatigue, nausea, upper abdominal mass, jaundice, fever, and other symptoms may appear, although jaundice is less common. Perihilar and distal bile duct cancers often involve bile duct obstruction, leading to obstructive jaundice. Jaundice worsens gradually over time, accompanied by pale or grayish-white stools, dark yellow urine, and pruritus. Patients commonly experience fatigue, weakness, and weight loss, with overall systemic symptoms. Right upper abdominal pain, chills, and fever indicate the presence of cholangitis.

Laboratory investigations

Blood tests: No blood tests are diagnostic for BTC. In the presence of bile duct obstruction, liver function tests indicate elevated bilirubin, alkaline phosphatase, and gamma-glutamyl transferase concentrations. Transaminases may also be elevated, and in the presence of bile duct inflammation, the concentrations of these enzymes can increase dramatically. Prolonged biliary obstruction can lead to decreased fat-soluble vitamin concentrations (i.e., A, D, E, and K) and prolonged prothrombin time. As the disease progresses, albumin, hemoglobin, and lactate dehydrogenase concentrations may decrease.

Serum tumor markers: BTC lacks specific tumor markers, with carbohydrate antigen 19-9 (CA19-9), CA125, and carcinoembryonic antigen (CEA) having some value. CA19-9: Approximately 85% of BTC patients have elevated CA19-9 concentrations. Elevated CA19-9 can also be seen in obstructive jaundice due to other reasons. However, continuing increases in CA19-9 concentrations after biliary drainage suggests BTC. Elevated CA19-9 can also be associated with pancreatic and gastric malignancies, and severe liver damage. CA125: Approximately 65% of BTC patients have elevated CA125 concentrations. CEA: Approximately 30% of BTC patients have elevated CEA concentrations. However, elevated CEA can also be observed with intestinal inflammation, benign biliary obstruction, gastrointestinal tumors, and severe liver damage.

Liquid biopsy: For patients with a high risk of recurrence, and with tumor monitoring during treatment of advanced cholangiocarcinoma, liquid biopsy might be considered.

Imaging

Abdominal multiphasic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) is suggested for the diagnosis and follow-up of BTC. Chest CT, with or without contrast, and pelvic multiphasic contrast-enhanced CT or MRI is suggested for staging and follow-up. MR cholangiopancreatography is preferred for evaluation of the extent of biliary involvement. Positron emission tomography/CT may be considered when economic conditions permit; the high specificity is important for differential diagnosis when there is an equivocal finding.^[38,39] Imaging for staging is suggested prior to biopsy or biliary drainage.

Diagnostic endoscopy

Endoscopic retrograde cholangiopancreatography (ERCP)-brushing/biopsy is the main approach for the histological diagnosis and molecular profiling of eCCA. When cross-sectional imaging and ERCP findings are inconclusive, peroral cholangioscopy (POC) and endoscopic ultrasonography with fine needle aspiration or biopsy (EUS-FNA/FNB) are useful to discriminate benign and malignant biliary strictures. POC could be used for direct visualization and targeted biopsy, while EUS-FNA/FNB could facilitate the evaluation of locoregional extension and be used to identify metastatic lymph nodes.

Clinical question 1: In patients with undetermined biliary strictures (UBS), could ERCP combined with POC versus ERCP alone improve the ability to diagnose malignancies?

Recommendation 1: We recommend ERCP combined with POC for patients with UBS, that could improve the diagnostic yields over ERCP alone (strong recommendation, high certainty of evidence).

Patients with UBS often pose a diagnostic and therapeutic dilemma owing to the limited sensitivity of conventional diagnostic modalities.^[40] Definitive and timely diagnosis of UBS is of great importance to guide optimal management. Providing both direct visualization and targeted biopsy, POC has higher sensitivity and leads to fewer repeat interventions without an increase in AEs compared with ERCP alone. Additionally, endoscopists encounter no additional technical difficulties, especially for ERCP experts. Furthermore, the new generation single-operator POC (S-POC) models, which have higher resolution, greater flexibility, larger working channel (maximum 2.0 mm), and lower cost compared with earlier models, may further improve the incremental benefits and popularity of POC.

A recently published meta-analysis (13 studies, 876 patients) demonstrated the high performance of POC for UBS, with an overall sensitivity of 88% (95% confidence interval [CI]: 0.83–0.91) and specificity of 95% (95% CI: 0.89–0.98).^[41] In 2020, Gerges *et al*^[42] reported the first comparative randomized controlled trial (RCT) of POC *vs.* ERCP and reported that the sensitivity of POC-biopsy was significantly higher than that of ERCP-brushing (68.2% *vs.* 21.4%, $P < 0.01$). POC also had higher

sensitivity and overall accuracy of visual diagnosis for malignancy *vs.* ERCP (95.5% *vs.* 66.7%, $P = 0.02$; 87.1% *vs.* 65.5%, $P = 0.05$). Mild AEs occurred in five patients, and no significant difference was found between the groups (POC: 6.5% *vs.* ERCP: 10.3%; $P = 0.59$). A large retrospective study involving 614 patients obtained similar results, reporting that POC had an incremental yield of 22.9%–51.9% higher sensitivity *vs.* ERCP.^[43] With another four observational studies for meta-analysis, the incremental yield of additional POC was at least 27%.^[42,44–47]

Currently, digital S-POC is used most commonly, clinically, and requires no additional expertise over ERCP. The technical success rate of S-POC (digital or fiberoptic) was 87%–100% for malignant biliary stricture, while digital S-POC had the highest success rate of the diagnostic options, at 100%.^[48] A recent prospective national study of digital S-POC from Italy^[49] reported a technical success rate of 97.6% (360/369). The AE rate was 10.4%, with no severe AEs. Although direct cost-effective analysis of POC for UBS is lacking, POC eliminated the need for repeat procedures and may be more cost-effective *vs.* ERCP.^[50] Multiple guidelines and consensus statements also recommend POC for UBS.^[40,47,51–54] The new generation Chinese S-POC, which has better performance and a lower price compared with earlier versions, may promote the popularity of POC.

Clinical question 2: What is the role of EUS-FNA/FNB in diagnosing biliary malignancies?

Recommendation 2: EUS-FNA/FNB could be considered an option for diagnostic tissue sampling of suspected biliary malignancies or regional metastatic lymph nodes, especially when the results of conventional ERCP-brushing/biopsy are negative or inconclusive (weak recommendation, moderate certainty of evidence).

The reported incremental benefit of EUS was 14% over ERCP, which is most beneficial for patients with distal strictures or extrinsic masses.^[55] With a pooled AE rate of 0.5%, EUS had comparable safety to that of ERCP.^[56] Additionally, EUS-FNA/FNB can distinguish malignancies from enlarged lymph nodes, which would have a major impact on clinical decision-making and prognosis. Given the similar sensitivity to that of ERCP, EUS equipment accessibility and local expertise, and concerns over needle tract seeding, some experts do not recommend routine EUS, or a combination of ERCP and EUS in the same session to diagnose biliary malignancies.

A 2022 meta-analysis (32 studies, 1123 patients)^[56] showed that the pooled diagnostic sensitivity of EUS-FNA and ERCP-brushing/biopsy for cholangiocarcinoma were 73.6% (95% CI: 64.7%–81.5%) and 70.7% (95% CI: 64.1%–76.8%), which were both much higher sensitivities than that with ERCP-brushing alone (56.0%, 95% CI: 48.8%–63.1%). The AE rate of EUS-FNA in tissue acquisition was 0.5% (95% CI: 0.1%–1.2%), comparable to that of ERCP. When conventional ERCP is nondiagnostic, EUS could provide an incremental benefit of 14% (95% CI: 7%–20%).^[55] For patients with undetermined distal

or extrinsic strictures, the incremental benefit increases to 38% (60%–98%) and 29% (68%–97%), respectively.^[55,57,58]

EUS-FNA/FNB also helps identify metastatic lymph nodes. A 2020 retrospective study from the Mayo Clinic indicated that EUS had a higher detection rate of regional lymph nodes than that with cross-sectional imaging (86% *vs.* 47%, $P < 0.01$).^[59] The sensitivity of EUS-FNA was 87.1% (27/31) in identifying metastatic lymph nodes. Surgical exploration was prevented in 14% (20/141) of patients with potentially resectable pCCA because of malignant lymph nodes identified by EUS-FNA/FNB.^[60] Despite some endoscopists' favoring routine EUS,^[59,60] experts on the panel preferred its conditional use, depending on local equipment and expertise availability, lesion location, and initial ERCP results. The conditional use of EUS-FNA/FNB for cholangiocarcinoma was also suggested by some guidelines and consensus statements.^[47,53,61,62]

Principles of pathological diagnosis

BTC pathological specimens are mainly derived from radical resection, exploratory laparotomy, exfoliated cells in bile drainage, biliary cell brushing guided by ERCP, choledochoscopy biopsy, FNA, or percutaneous biopsy guided by B-ultrasonography or CT. Pathological diagnosis is recommended in accordance with *the fifth edition of the WHO Classification of Digestive System Tumors*. In the pathological evaluation of radical treatment specimens of malignant biliary tract tumors, the pathological type of the tumor, histological subtype, degree of differentiation, tumor size, distribution of the tumor in the bile duct and/or gallbladder, degree of tumor invasion, vascular invasion, nerve invasion, surgical margins, lymph node metastasis, and intrahepatic and distant metastasis should be diagnosed. The recommended number of lymph nodes detected in iCCA and GBC should be ≥ 6 , while the number should be ≥ 12 for dCCA. Regarding biopsy pathological specimens, attempting an accurate pathological diagnosis of biopsy cells or tissues is often decisive in the diagnosis and treatment of tumors. Therefore, the nature of the lesion should be clarified as much as possible. If possible, techniques including liquid-based cells, special stains, immunohistochemistry, and molecular pathology (such as fluorescence *in situ* hybridization [FISH] ploidy detection^[63]), can be used to further clarify the diagnosis of tumor pathological properties, subtypes, and degree of differentiation. The liver is a common metastatic organ for numerous malignant tumors. When diagnosing iCCA, special attention should be paid to the differential diagnosis from metastatic adenocarcinoma derived from other organs. Currently, commonly used immunohistochemical indicators can help in the identification. If necessary, these methods can be combined with clinical practice or multidisciplinary team discussions to help identify the origin of the tumor. However, there will still be cases for which it is difficult to identify the origin pathologically.

Immunohistochemistry is helpful in the pathological differential diagnosis of cholangiocarcinoma, biliary adenocarcinoma (cytokeratin [CK]7 and CK19 are

usually positive, while CK20 is usually negative), small cholangiocarcinomas (cluster of differentiation [CD]56+), squamous cell carcinoma (P40, P63+), and neuroendocrine carcinoma (synaptophysin and chromogranin A+). Additionally, immunohistochemistry can detect some targets of targeted therapy and immunotherapy, including programmed death ligand-1 (PD-L1), PD-1, c-MET, epidermal growth factor receptor, human epidermal growth factor receptor 2 (HER2), MLH1, MSH2, MSH6, and PMS2. MLH1, MSH2, MSH6, and PMS2 protein expression detection can determine mismatch repair (MMR) status, and molecular detection, such as microsatellite instability (MSI) can also be performed. For iCCA, especially mass-type iCCA, it is recommended to perform FGFR2 breakage probe FISH detection and isocitrate dehydrogenase (IDH)1/2 sequencing to detect whether there are related gene mutations.

Additionally, if conditions permit, FISH detection; c-MET, HER2, and NTRK1-3 first-generation sequencing; and BRCA1/2 and BRAF next-generation sequencing can be performed.^[64–66]

Treatment

Surgical treatment

pCCA

Radical R0 resection is the only curative method to achieve potential cure in patients with pCCA. Intraoperative frozen section of the bile duct margin is recommended to confirm negative margins. Wide liver resection combined with extrahepatic bile duct resection can enhance the R0 resection rate.

Surgical approach: Appropriate surgical approach could be selected by different tumor types. (1) Bismuth type I and II with tumor not invading the opening of the terminal bile duct: Patients can undergo perihilar bile duct tumor resection; (2) Bismuth type II located at the bifurcation of the bile duct requires combined resection of liver segment S4b with left or right lobectomy; (3) Type IIIa requires right lobectomy, while type IIIb requires left lobectomy; and (4) Type IV requires central liver resection or expanded left/right lobectomy, with concurrent removal of the entire terminal bile duct, as for Bismuth types II, III, and IV.

Lymph node dissection range: Lymph node metastasis is a crucial prognostic factor in BTC. Patients with negative lymph nodes have a 5-year survival rate of 30%, whereas the survival rate for those with localized lymph node metastasis decreases to 15% and is 12% in those with para-aortic lymph node metastasis. The lymph node dissection range includes lymph nodes within the hepatoduodenal ligament (12 groups), lymph nodes behind the pancreatic head (13 groups), and lymph nodes beside the hepatic artery (8 groups). If para-aortic lymph nodes are positive, surgery is not indicated.

Biliary reconstruction method: Classic choledochenterostomy using Roux-en-Y anastomosis is recommended

for biliary reconstruction. After liver resection, if multiple bile duct openings are present, it is advisable to integrate the openings through bile duct shaping surgery to reduce the number of anastomosis sites and prevent bile leakage and anastomotic stenosis. Smaller diameter bile ducts can accommodate drains.

Vascular resection and reconstruction: Resection and reconstruction of the portal vein or hepatic artery during surgery can increase the R0 resection rate. For cases in which R0 resection is achieved through hepatic artery or portal vein resection, combined vascular reconstruction could be considered.

Minimally invasive surgery: Some type I and II pCCAs can be managed via laparoscopic bile duct resection, partial liver resection, bile-intestinal anastomosis, and perihilar lymph node dissection. Laparoscopic or robot-assisted surgery for pCCA demands high surgeon proficiency and is highly complex. Currently, the widespread adoption of this approach is limited, awaiting further exploration through extensive case studies.

Clinical question 3: Is routine combined liver caudate lobe resection required in patients with pCCA?

Recommendations 3: Patients with types II, and III, and IV pCCA with caudate lobe bile duct invasion require combined caudate lobe resection (strong recommendation, high certainty of evidence).

In patients with pCCA, the scope of resection is controversial, primarily regarding the different surgical methods.^[67] Current review and meta-analyses suggest that combined caudate lobectomy can increase the radical resection rate (R0) without increasing perioperative risks, and improve long-term outcomes, so that combined caudate lobectomy is strongly recommended for patients with types II, III, and IV pCCA with invasion of the caudate bile ducts.^[68,69]

iCCA

Surgical approach: Radical resection is the main curative method for iCCA, and achieving R0 resection can enhance patient prognosis and reduce recurrence risk. Negative margins are required for both liver and bile duct edges. There is no consensus on the distance for bile duct margins.

Lymph node dissection: The lymph node metastasis rate in iCCA exceeds 30%, and lymph node metastasis is a significant prognostic indicator. Routine regional lymph node dissection is often performed (including hepatoduodenal ligament, hepatic artery, and peripancreatic head lymph nodes), with a minimum detection of no fewer than six lymph nodes.

Liver transplantation selection: Liver transplantation is the most promising treatment for patients meeting the transplantation criteria and with insufficient residual liver volume or abnormal liver function. However, strict exclusion of lymph node metastasis, vascular invasion, and extrahepatic bile duct invasion is necessary. For very early-stage (tumor <2 cm) iCCA with concomitant liver

cirrhosis, liver transplantation has shown promising treatment outcomes.

Clinical question 4: Is lymph node dissection necessary in patients with iCCA?

Recommendation 4: In patients with iCCA, routine lymph node dissection is recommended to provide accurate lymph node staging and guide postoperative comprehensive treatment (strong recommendation, weak certainty of evidence).

Currently, there are multiple systematic reviews and meta-analyses of lymph node dissection in patients with iCCA.^[70] Although the results indicate no improvement in prognosis, the proportion of patients who undergo lymph node dissection who have lymph node metastases is not low, and lymph node metastases is a high-risk factor affecting patient prognosis.^[71,72] Lymph node dissection is also important for accurate staging, which could help with prognosis-related risk assessment and guide comprehensive postoperative treatment.^[73,74]

GBC

Radical resection is a useful method to achieve complete cure in primary GBC.^[75] Thorough preoperative examination, assessment, and tumor-node-metastasis (TNM) staging aid in determining the scope of surgical resection. Surgery should be performed by an experienced hepatobiliary surgeon. For those with preoperatively diagnosed advanced-stage GBC or intraoperative biopsy-confirmed GBC, open radical cholecystectomy is suggested.

Surgical approach: For Tis and T1a GBC, simple cholecystectomy suffices, as these stages are often identified incidentally. T1b-stage GBC requires radical cholecystectomy, encompassing the gallbladder and a 2-cm margin of surrounding liver parenchyma; negative liver margins are required.^[76] T2 and T3N0 stages necessitate segment (S)4b + S5 liver resection. For T3N1-stage patients with tumors infiltrating the liver parenchyma by >2 cm, located at the gallbladder neck, invading the gallbladder triangle, or with lymph node metastasis, right hepatectomy or right trisectionectomy is indicated. T4-stage GBC patients without distant metastasis can undergo combined organ resection, including right hepatectomy or right trisectionectomy; however, radical cholecystectomy is not usually performed for those with distant metastasis.

Lymph node dissection range: Tis or T1a stage GBC does not necessitate regional lymph node dissection. For stage ≥T1b, dissection encompasses the hepatoduodenal ligament (12 groups), hepatic artery (8 groups), and peripancreatic head (13 groups) lymph nodes. If lymph node biopsy from group 8 or 13 indicates positive nodes, the range can be extended to the lymph nodes around the celiac trunk; however, surgery is not usually performed for positive group 16 lymph nodes. A minimum of six lymph nodes should be dissected for GBC.

Management of affected extrahepatic bile duct: Combining extrabiliary hepatic duct resection to increase the

lymph node dissection count is not advised as doing so does not enhance survival. For patients with jaundice and gallbladder duct cancer or gallbladder neck cancer involving the extrabiliary hepatic duct, combined extrabiliary hepatic duct resection can be performed, ensuring negative margins for R0 resection, followed by hepaticojejunostomy.

Combined organ resection and vascular reconstruction:

For stage T4 GBC without distant metastasis infiltrating surrounding organs, extended radical surgery can be performed, including combined extrabiliary hepatic duct resection, right trisectionectomy, portal vein resection and reconstruction, right hemicolectomy, and pancreaticoduodenectomy. Portal vein involvement is the sole obstacle to R0 resection in GBC. For this, radical surgery with combined portal vein resection and reconstruction can be considered; otherwise, surgical bile duct drainage could be used.

Clinical question 5: In patients with resectable GBC, can anatomical liver resection on the basis of TNM staging improve the radical (R0) resection rate?

Recommendation 5: In patients with resectable GBC, anatomical liver resection on the basis of TNM staging is suggested to ensure negative liver margins (weak recommendation, low certainty of evidence).

The incidence of GBC is low; therefore, it is difficult to perform large-scale prospective studies. Currently, most studies are retrospective with small sample sizes, which may easily lead to bias. In high-incidence areas, such as China, Chile, India, and Southeast Asia, GBC treatment is not sufficiently standardized, especially regarding the lack of postoperative comprehensive treatment. Therefore, some multicenter studies have selection bias.^[77,78] Previous retrospective case-control studies have shown that in resectable patients with GBC, anatomical liver resection on the basis of TNM staging can effectively improve the radical (R0) resection rate.^[79–82]

dCCA

Radical R0 resection is effective to achieve a cure. Intraoperative frozen pathology examination of bile duct margins and pancreatic duct margins is necessary to confirm the absence of tumor involvement.

Surgical approach: For distal bile duct cancer, pancreaticoduodenectomy could be used with confirmed negative margins. In early-stage distal bile duct cancer, laparoscopic and robotic-assisted surgeries show no significant differences in long-term efficacy compared with open surgery, but laparoscopic and robotic-assisted approaches offer clear advantages in terms of postoperative rapid recovery.

Lymph node dissection: The regional lymph node dissection scope includes lymph nodes within the hepatoduodenal ligament, lymph nodes in front of and behind the pancreas and duodenum, as well as lymph nodes on the right side of the superior mesenteric artery. To accurately determine the N stage, it is suggested to dissect a minimum of 12 lymph nodes.

Among patients with advanced cholangiocarcinoma, hepatopancreaticoduodenectomy (HPD) has a high complications rate and should be performed in high-volume hospitals. Patients are expected to achieve R0 resection and potential long-term survival after rigorous preoperative evaluation. HPD might be considered an option for those for whom R0 resection is achievable.

Clinical question 6: What is the efficacy and safety of perioperative early release after surgery (ERAS) in patients with BTC?

Recommendation 6: In patients with cholangiocarcinoma, perioperative ERAS can help improve perioperative safety, shorten postoperative hospitalization time, and reduce the incidence of perioperative complications (strong recommendation, moderate certainty of evidence).

Few high-quality systematic reviews, meta-analyses, or RCTs have evaluated perioperative ERAS in BTC. However, there are numerous systematic reviews, meta-analyses, and clinical guidelines for upper gastrointestinal surgery, pancreaticoduodenectomy, and hepatectomy recommending ERAS, and most surgical methods for bile duct cancer are included.^[83–85] High-quality clinical studies of perioperative ERAS in BTC should be performed to improve the level of evidence.

Perioperative treatment

Endoscopic treatment for jaundice

The details are shown in the section of “Endoscopic treatment”.

Interventional therapy for jaundice

Percutaneous transhepatic cholangial drainage (PTCD) could be actively performed for patients who do not receive endoscopic drainage or cannot receive endoscopic drainage for jaundice reduction owing to poor general condition. PTCD is easy to perform and convenient for drainage of multiple bile ducts. ERCP is not very effective in the treatment of Bismuth–Corlette IV hCCA, mainly because of the high location of the obstruction, multi-branch bile duct involvement, and capillary obstruction around bile ducts. For such patients, PTCD or ERCP with PTCD could reduce jaundice because ultrasound-guided puncture can be performed in the proximal bile duct. In principle, the bile ducts of the preserved liver should be reserved for PTCD. Although related complications, such as pancreatitis, caused by ERCP can be avoided, PTCD has the associated risks of puncture bleeding, needle-tract implantation, and electrolyte disturbance caused by external bile drainage, intraoperatively. Collected bile can be transfused, if possible, to avoid these risks. For patients who require long-term drainage, biliary stent implantation via PTCD is often used to reduce body fluid loss.

Clinical question 7: Could preoperative biliary drainage improve the perioperative safety of patients with jaundice?

Recommendation 7: Patients with cholangitis, serum bilirubin concentrations $>200 \mu\text{mol/L}$, and large liver resections (greater than 60%) are recommended to receive preoperative therapy to decrease bilirubin concentrations (strong recommendation, moderate certainty of evidence).

Although there are some inconsistencies in the conclusions of previous systematic reviews and meta-analyses,^[86–88] the results of subgroup analysis in relevant studies, with eligible single-arm and retrospective clinical studies, as well as domestic and international guidelines and expert consensus statements,^[89,90] recommend that preoperative reduction of bilirubin in patients with cholangitis, serum bilirubin concentrations $>200 \mu\text{mol/L}$, and the need for extensive liver resection can reduce postoperative complications. Large-scale multicenter RCTs are needed to provide further evidence.

Nutritional support

Owing to the important functions of the biliary system in collecting and transporting bile, most patients with biliary malignancies have the risk of malnutrition perioperatively. Preoperative nutritional therapy can reduce morbidity associated with postoperative complications. Therefore, nutritional assessments and nutritional therapy are key components in preoperative preparation. *The Nutritional Risk Screening 2002 tool* for nutritional risk screening and *Patient-Generated Subjective Global Assessment* for nutritional assessment of patients with malignant tumors can be used. The appropriate nutritional route can be intravenous or enteric (oral, tube feeding). Biliary tract surgery causes less damage to the lower gastrointestinal tract compared with other gastrointestinal surgeries. Therefore, placing a jejunal feeding tube or creating a jejunostomy is often performed in patients who require postoperative nutritional support. For patients with excessive bile loss, bile autoinfusion combined with enteral nutrition could be considered to improve gastrointestinal function.

Improving blood coagulation function

Patients with biliary tract tumors may have varying degrees of coagulation disorder before surgery owing to the combination of liver function damage and obstructive jaundice. Improving the patient's coagulation status and correcting existing coagulation abnormalities before surgery can effectively reduce intraoperative bleeding and blood product consumption; thereby improving perioperative safety.

Management of postoperative complications

Biliary fistula: Postoperative biliary fistulas in malignant tumors of the biliary tract are often caused by lax management of the bile duct after liver resection and leakage at the biliary intestinal anastomosis. The treatment of postoperative biliary fistula mainly comprises the following: (1) Routine treatment: With anti-infection medications, nutritional support, and the maintenance of water, electrolyte, and acid-base balance, some biliary fistulas can self-heal through effective abdominal drainage; (2)

Percutaneous biliary drainage: This is the foundation for treating biliary fistula; and (3) Surgical treatment: When conventional treatment and minimally invasive treatment are ineffective and the patient's condition deteriorates, abdominal surgery is the only option. The surgery mainly involves lavage to remove bile in the abdominal cavity, establishing sufficient external drainage, and determining and appropriately repairing the fistula.

Pancreatic fistula: Partial pancreaticoduodenectomy is the main cause of postoperative pancreatic fistula in some patients with bile duct tumors. Treatments of clinical pancreatic fistula include non-surgical treatment (drainage, infection control, and nutritional support) and surgical treatment (when non-surgical treatment is ineffective).

Postoperative bleeding: Non-surgical treatment can be considered for mild early postoperative bleeding while closely observing the patient's clinical signs and symptoms. For moderate to severe early abdominal bleeding, surgical treatment is often performed. If gastrointestinal bleeding or delayed bleeding is suspected, vascular intervention, endoscopy, and surgery if necessary, could be selected on the basis of technical capability and the presence of stable hemodynamics.

Chylous fistula: Chylous fistula is a postoperative complication in patients with malignant biliary tumors. The main treatment measures include: (1) dietary control: fasting combined with total parenteral nutritional support can effectively reduce the amount of chyle and the duration of the fistula; (2) use of somatostatin and its analogs; and (3) interventional and surgical treatment including puncture and drainage, embolization to achieve lymphatic sclerosis, abdominal vein bypass surgery, and lymphatic angiography combined with surgical ligation.

Abdominal infection: Postoperative abdominal infections and abscesses in malignant biliary tumors are usually caused by pancreatic or biliary fistulas. Broad-spectrum antibiotics are preferred as initial empirical therapy. Multiple samples including the drainage fluid, infected tissue, or blood for bacterial culture can eliminate contaminated bacteria, determine the possible pathogenic bacterial spectrum, and perform drug sensitivity tests to guide antibacterial treatment. Puncture and drainage performed as soon as possible, or open surgery if necessary, could address abdominal fluid accumulation and abscess.

Hepatic insufficiency and liver failure: This is a serious complication after liver resection, often related to uncorrected preoperative liver function, excessive liver resection volume, excessive blood loss during anesthesia, and prolonged hepatic portal occlusion time. Active improvement of coagulation function, and if necessary, administration of fibrinogen or prothrombin complex and other anticoagulant drugs will benefit.

Systemic therapy

BTCs present with minimal symptoms, and nearly two-thirds of patients with these tumors present with advanced disease at diagnosis. Additionally, in 68%–86% of

resections, the cancer eventually recurs either locoregionally or at a distance. Thus, systemic therapy that includes neoadjuvant therapy, adjuvant therapy, first-line (i.e., the first systemic therapy after the diagnosis of advanced cancer) and second-line therapy (i.e., replacement systemic drugs for patients who experience tumor progression after first-line treatment), and immunotherapy and targeted therapy play essential roles in the treatment of BTCs.^[91]

Clinical question 8: What is the effectiveness of neoadjuvant therapy for BTC?

Recommendation 8.1: For patients with borderline resectable and locally advanced BTC, preoperative chemotherapy or radiochemotherapy is suggested to permit surgical treatment and improve survival (weak recommendation, low certainty of evidence).

Recommendation 8.2: For patients with resectable BTC, there is currently insufficient evidence to suggest that neoadjuvant chemotherapy could improve survival (weak recommendation, low certainty of evidence).

The current recommendation is based on small-sample prospective and retrospective clinical studies.^[92–101] Currently, there is insufficient evidence to recommend neoadjuvant therapy. However, preoperative chemotherapy is suggested for patients with borderline resectable and locally advanced BTC to allow for surgery. Chemotherapy options mainly involve first-line treatment with a high objective response rate. Studies are currently being performed, with varying results that are worth anticipating. There is little direct RCT evidence to support chemotherapy, and high-quality RCTs are needed to resolve these issues.

Clinical question 9: What is the effectiveness and safety of adjuvant chemotherapy for BTC?

Recommendation 9: Adjuvant chemotherapy is recommended after resection for patients with BTC (strong recommendation, high certainty of evidence).

The current recommendation is based on the results of two RCTs. The BILCAP study was a randomized, controlled, multicenter, phase III study. In the intention-to-treat analysis, median overall survival was 51.1 months in the capecitabine group compared with 36.4 months in the observation group ($P = 0.097$).^[102] The JCOG1202 trial was an open-label, multicenter, randomized, phase III trial. The 3-year overall survival rate was 67.6% in the observation group compared with 77.1% in the S-1 group ($P = 0.008$).^[103] Furthermore, many studies have provided evidence supporting the effect of adjuvant chemotherapy.^[104–112] With these studies, many regimens could be chosen as adjuvant chemotherapy.

Clinical question 10: What is the recommended first-line treatment to improve the survival of patients with BTC?

Recommendation 10.1: Patients with advanced BTC can receive suitable first-line systemic treatment regimens on the basis of the patient's performance status (PS) (strong recommendation, high certainty of evidence).

Recommendation 10.2: For patients with good PS (0–1), gemcitabine combined with cisplatin and durvalumab, gemcitabine combined with cisplatin and pembrolizumab, gemcitabine combined with cisplatin and S-1, gemcitabine combined with cisplatin, and gemcitabine combined with S-1 are recommended (strong recommendation, high certainty of evidence). Furthermore, many other regimens also demonstrated potential therapeutic efficacy. The following could be considered: folinic acid + fluorouracil (FU) + irinotecan + oxaliplatin (mFOLFIRINOX); nanoparticle albumin-bound (nab)-paclitaxel plus gemcitabine; gemcitabine and cisplatin (GP) plus durvalumab with tremelimumab; nab-paclitaxel combined with GP; gemcitabine + oxaliplatin (GEMOX) combined with toripalimab and lenvatinib; and GEMOX combined with donafenib and tislelizumab (weak recommendation, moderate certainty of evidence).

Recommendation 10.3: For patients with acceptable PS (1–2), the following can be considered: gemcitabine combined with oxaliplatin; capecitabine combined with oxaliplatin (strong recommendation, high certainty of evidence); especially for KRAS wild-type patients; gemcitabine combined with oxaliplatin and erlotinib (strong recommendation, high certainty of evidence); and gemcitabine combined with oxaliplatin and panitumumab (weak recommendation, moderate certainty of evidence).

Recommendation 10.4: For patients with poor PS (>2), gemcitabine monotherapy; capecitabine monotherapy; 5-FU monotherapy; or S-1 monotherapy can be considered (strong recommendation, high certainty of evidence).

The recommendations are based on the results of six phase III RCTs. According to the ABC-02 study, GP is a standard first-line treatment regimen.^[113] According to the JCOG1113/FUGA-BT study, the efficacy of gemcitabine combined with S-1 (GS) is not inferior to the GP regimen.^[114] According to Kim *et al.*,^[115] capecitabine combined with oxaliplatin (XELOX) is not inferior to GEMOX and can also be recommended as a first-line treatment. According to the KHBO1401-MITSUBA study, gemcitabine, cisplatin plus S-1 (GCS) is superior to the GP regimen and may be a new first-line standard chemotherapy regimen for advanced BTC.^[116] According to the TOPAZ-1 trial, the combination of duvalizumab and GP is superior to the GP regimen and can be a first-line standard regimen for advanced BTC patients.^[117] According to the KEYNOTE-966 study, the combination of pabrolizumab and GP is superior to GP alone, and can be used as a first-line standard regimen for advanced BTC patients.^[118] There are multiple other studies in the phase II and exploratory stages, and the results are anticipated.^[115,119–129]

Clinical question 11: What is the recommended second-line treatment to improve the survival of patients with BTC?

Recommendation 11.1: Patients with advanced BTC can receive appropriate second-line systemic treatment regimens on the basis of their PS to improve survival (strong recommendation, high certainty of evidence).

Recommendation 11.2: For patients with good PS (0–1) who receive GP chemotherapy as first-line therapy, 5-FU combined with oxaliplatin (strong recommendation, high certainty of evidence), 5-FU combined with liposomal irinotecan (strong recommendation, moderate certainty of evidence), regorafenib (weak recommendation, moderate certainty of evidence), and trametinib (weak recommendation, low certainty of evidence) could be considered, as well as S-1 and 5-FU (weak recommendation, low certainty of evidence).

Recommendation 11.3: For patients with acceptable PS (1–2) who receive GP chemotherapy as first-line therapy, modified 5-FU combined with irinotecan or modified 5-FU combined with oxaliplatin could be considered (weak recommendation, moderate certainty of evidence).

Recommendation 11.4: For patients with poor PS (>2) who receive gemcitabine as first-line therapy, irinotecan monotherapy may be considered, with efficacy not inferior to that of capecitabine combined with irinotecan chemotherapy (weak recommendation, moderate certainty of evidence); capecitabine monotherapy may be considered (weak recommendation, moderate certainty of evidence).

The current recommendation is based on the results of RCTs. According to the ABC-06 study, FOLFOX should become the standard chemotherapy regimen for second-line treatment of advanced biliary cancer.^[130] According to the NIFTY study results, liposome irinotecan combined with 5-FU and folic acid can be considered an important second-line option for advanced biliary cancer.^[131] Additionally, there are some clinical studies with relatively low levels of evidence, and further studies are worthwhile.^[132–139]

Clinical question 12: Can the survival of patients with advanced BTC with specific gene mutations be improved by targeted therapy?

Recommendation 12.1: For some patients with advanced BTC with specific genetic mutations, specific targeted drugs are recommended after standard treatment failure, which can improve survival (strong recommendation, high certainty of evidence).

Recommendation 12.2: For the presence of *NTRK* gene fusion, entrectinib or lorlatinib can be chosen after standard treatment failure (strong recommendation, high certainty of evidence).

Recommendation 12.3: For the presence of *RET* gene fusion, selpercatinib or pralsetinib can be selected after standard treatment failure (strong recommendation, high certainty of evidence).

Recommendation 12.4: For the presence of *FGFR2* gene fusion or rearrangement, after standard treatment failure, pemigatinib, infigratinib, futibatinib (strong recommendation, high certainty of evidence), erdafitinib (weak recommendation, moderate certainty of evidence), and derazantinib could be selected (weak recommendation, low certainty of evidence).

Recommendation 12.5: For patients with *BRAF-V600E*, dabrafenib combined with trametinib could be chosen after standard treatment failure (weak recommendation, low certainty of evidence).

Recommendation 12.6: For patients with *IDH1* mutations, ivosidenib can be chosen after standard treatment failure (strong recommendation, high certainty of evidence).

Recommendation 12.7: For *HER2*-positive patients, after standard treatment failure, the combination of pertuzumab and trastuzumab could be considered (weak recommendation, low certainty of evidence).

The current recommendation is based on the results of clinical trials guided by eligible biomarkers, with specific genetic variations, namely *FGFR2* rearrangement/gene fusion, *IDH1* mutation, *NTRK* gene fusion, *RET* gene fusion, *HER2*-positive status, and *BRAF-V600E* mutation.^[121,140–152] There are also clinical studies with relatively low levels of evidence, and further research is warranted.

Clinical question 13: Can the survival of patients with advanced BTC be improved by immunotherapy?

Recommendation 13.1: In the first-line systemic treatment of advanced BTC, for patients with good PS, gemcitabine combined with cisplatin and durvalumab, or gemcitabine combined with cisplatin and pembrolizumab can be considered (strong recommendation, high certainty of evidence).

Recommendation 13.2: For patients with dMMR/MSI-H, immunotherapy alone can be considered (strong recommendation, high certainty of evidence).

The current recommendation is based on the results of RCTs. According to the TOPAZ-1 trial, first-line treatment with gemcitabine, cisplatin, and duvalizumab can significantly prolong the survival of patients with unresectable or metastatic BTC.^[117,153] According to the results of the KEYNOTE-966 trial, the first-line treatment of unresectable or metastatic BTC with gemcitabine, cisplatin, and pembrolizumab can significantly prolong survival.^[118] For unresectable or metastatic BTC with dMMR/MSI-H gene mutations, single PD-1 inhibitors have good therapeutic effects.^[154] There are also clinical studies with relatively low levels of evidence, and further research is warranted.^[155–158]

Radiotherapy

With rapid developments in modern radiotherapy techniques, this modality plays an important role in patients with various stages of BTC. Intensity-modulated radiotherapy is now widely used in different medical centers. Stereotactic body radiotherapy (SBRT) has recently gained attention because of the advantage of dose distribution, which is dependent on the tumor location and the limited doses to adjacent organs at risk (OAR). Additionally, some small-sample studies suggested that hypofractionated

proton beam radiotherapy can achieve good local control for patients with BTC; phase III clinical trials are in progress.^[159] On the basis of different treatment purposes, radiotherapy can be classified into four categories: adjuvant radiotherapy, neoadjuvant radiotherapy, radical radiotherapy, and palliative radiotherapy.

Adjuvant radiotherapy

Surgery is the main radical treatment for patients with BTC, but the prognosis is relatively poor, especially for patients with high-risk factors. A prospective phase II study (SWOG S0809) and some meta-analyses showed significant survival benefits of adjuvant radiotherapy for patients with eCCA or GBC and high-risk factors (R1 resection and/or positive lymph nodes).^[110,160–167] Adjuvant radiotherapy is suggested to begin within 8 weeks after surgery or after 2–4 cycles of adjuvant chemotherapy. The clinical target volume (CTV) of adjuvant radiotherapy could include the tumor bed and draining regional lymph nodes. The planning target volume is created by expanding CTV with 3–5-mm uniform margins. The suggested radiation dose is 45.0–50.4 Gy as 1.8–2.0 Gy per fraction to draining regional lymph nodes, and 54–60 Gy as 1.8–2.0 Gy per fraction to the tumor bed, depending on the resection margin positivity and the limited doses of OAR.^[168,169]

Neoadjuvant radiotherapy

Neoadjuvant radiotherapy is an option for patients with BTC and a high risk of recurrence. Some retrospective studies found that neoadjuvant chemoradiotherapy could achieve tumor downstaging and OS improvement with no increase in surgical-related complications.^[93,170,171] Radiotherapy can also transform some unresectable BTCs to resectable.^[94,172] However, the recommendation of neoadjuvant radiotherapy for patients with BTC is based on small-sample studies, with a lack of high-level evidence, and rigorous screening and further exploration is necessary. The CTV of neoadjuvant radiotherapy could include the primary lesion and metastatic lymph nodes, and may include high-risk draining regional lymph nodes. The PTV is determined by expanding the CTV with 3–5-mm uniform margins. The suggested radiation dose is 45.0–50.4 Gy as 1.8–2.0 Gy per fraction. SBRT is an option when the tumor size is small and there is no lymph node metastasis. Dose segmentation of 40 Gy as 8 Gy per fraction could be considered according to the UCLA Cancer Center.^[173]

Radical radiotherapy for locally advanced BTC

The efficacy of chemotherapy alone is relatively poor for patients with locally advanced BTC. Numerous retrospective studies consistently showed that chemoradiotherapy could improve OS significantly compared with chemotherapy alone.^[174–182] Conventional radiotherapy is suggested when there is a large target volume. The suggested radiation dose is 45.0–50.4 Gy as 1.8–2.0 Gy per fraction; ≥ 60 Gy is considered to the gross tumor volume if the doses to the OAR meet the limits. SBRT could be considered when

the lesion is relatively small,^[183,184] and a biologically effective dose of >80.5 Gy is suggested if the doses to the OAR meet the limits. The dose segmentation can be administered as 30–50 Gy as 3–5 fractions or 67.5 Gy as 15 fractions.^[185] Concurrent fluoropyrimidine-based chemotherapy (fluorouracil or capecitabine) is suggested, and concurrent gemcitabine can also be considered.^[186]

Palliative radiotherapy

For patients with advanced BTC, palliative radiotherapy can relieve symptoms and improve local control. The target volume and dose of palliative radiotherapy are based on the tumor burden, tumor location, and the patient's physical condition.

Clinical question 14: What is the effectiveness and safety of adding adjuvant radiotherapy to standard adjuvant chemotherapy for BTC after surgery in patients with high-risk factors?

Recommendation 14: Adjuvant radiotherapy is recommended for eCCA or GBC after surgery in patients with high-risk factors (R1 resection and/or positive lymph nodes) (strong recommendation, moderate certainty of evidence).

The current recommendations are based on the results of RCTs, single-arm clinical studies, and meta-analyses of observational studies. For patients with eCCA or GBC and high-risk factors (R1 resection and/or positive lymph nodes) after surgery, the addition of adjuvant radiotherapy can improve OS significantly, with consistent evidence. The side effects of adjuvant radiotherapy are tolerable, with high safety. Additionally, the costs of adjuvant radiotherapy are affordable and within the scope of medical insurance. The heterogeneity of the included population is high, with significant differences in tumor location, tumor stage, and ethnicity. However, there is little direct RCT evidence to confirm this recommendation; high-quality RCTs are needed.

SWOG S0809 is the only prospective, single-arm, phase II study of adjuvant radiotherapy for BTC after surgery.^[110] The study included patients with eCCA or GBC after radical resection, with stage pT2–4 cancer, or N+ or R1 resection. Patients received chemotherapy followed by concurrent capecitabine and radiotherapy. Seventy-nine eligible patients were treated (R0, $n = 54$; R1, $n = 25$). Median OS for all patients was 35 months; 34 months for R0 and 35 months for R1. Median disease-free survival for all patients was 26 months; 26 months for R0 and 23 months for R1. OS was significantly higher with adjuvant radiotherapy than without regarding the expected rates on the basis of historical controls. The most common grade 3–4 adverse effects were neutropenia (44%), hand-foot syndrome (11%), diarrhea (8%), lymphopenia (8%), and leukopenia (6%). A meta-analysis included 1465 patients with eCCA or GBC from 21 retrospective studies.^[162] The 5-year OS rate was higher in the adjuvant radiotherapy group than that in the no-radiotherapy group (odds ratio [OR]: 0.63; 95% CI: 0.50–0.81; $P = 0.0002$). The 5-year OS rate was significantly higher for patients with lymph

node-positive disease (OR: 0.15; 95% CI: 0.07–0.35; $P < 0.001$) and margin-positive disease (OR: 0.40; 95% CI: 0.19–0.85; $P = 0.02$) in the adjuvant radiotherapy group compared with the no-radiotherapy group. Three other meta-analyses performed subgroup analyses for lymph node- or resection margin-positivity, and consistently showed survival benefits with adjuvant radiotherapy for patients with eCCA or GBC and high-risk factors (R1 resection and/or positive lymph nodes).^[160,163,166]

Clinical question 15: Is the addition of radiotherapy to chemotherapy necessary for patients with unresectable locally advanced BTC?

Recommendation 15: For patients with unresectable locally advanced BTC, radiochemotherapy is recommended and could improve prognosis and quality of life (strong recommendation, low certainty of evidence).

For unresectable, non-metastatic locally advanced BTC, prospective studies confirmed the effectiveness and safety of chemoradiotherapy, and many large-sample retrospective studies also consistently showed survival benefits with chemoradiotherapy compared with chemotherapy alone. Radiotherapy is effective and safe, and the costs are within the scope of medical insurance. However, results from large-scale RCTs are still lacked.

Two prospective studies^[186,187] have confirmed the effectiveness and safety of chemoradiotherapy for patients with locally advanced BTC. However, the only prospective phase II RCT, FFCD-9902, was terminated early. Another prospective phase II clinical trial^[186] from Italy included 27 patients with unresectable, non-metastatic eCCA who received chemoradiotherapy (gemcitabine). The median OS was 14 months, the 2-year OS was 27%, the 2-year local control rate was 29%, and 37% of the patients suffered $\geq$ grade 3 acute toxicity. A large-sample analysis of the SEER database included 4027 patients with unresectable iCCA, 847 (21%) patients underwent radiotherapy, whereas 3180 did not. After propensity score matching, radiotherapy was associated with significantly better OS *vs.* no radiotherapy (adjusted hazard ratio [HR]: 0.8544, 95% CI: 0.7722–0.9453; $P = 0.002$) and cancer-specific survival (adjusted HR: 0.8563, 95% CI: 0.7711–0.9509; $P = 0.004$).^[174] An analysis of the National Cancer Database included 1636 patients with unresectable, localized iCCA who received chemotherapy, of which 23% also received radiotherapy. The 2-year OS was 26% and 20% for chemoradiotherapy and chemotherapy-alone groups, respectively ($P = 0.001$). Multivariate analysis showed that chemoradiotherapy remained significantly associated with improved OS (HR: 0.80, 95% CI: 0.71–0.91; $P = 0.001$).^[175] Another analysis of the National Cancer Database included 2966 patients with unresectable, non-metastatic eCCA and showed that chemoradiotherapy was associated with better survival compared with chemotherapy alone, with a median OS of 14.5 and 12.6 months, respectively (HR: 0.84; $P < 0.001$). The majority of the benefit was observed for patients able to undergo eventual surgery.^[176]

Endoscopic treatment

Endoscopic treatment could provide both biliary drainage as well as locoregional tumor treatment. For patients with severe obstructive jaundice, biliary drainage is common to improve hepatorenal function and prevent infection. The choice of drainage access (endoscopic or percutaneous) depends on the patient's condition, local expertise, tumor location, and follow-up treatment. It is worth noting that routine preoperative biliary drainage is not recommended and is only indicated in select patients after multidisciplinary consultation.^[188] Generally, for dCCA, ERCP is preferred, while for hCCA, the choice often depends on individual patient circumstances, and multidisciplinary collaboration is needed.

Radiofrequency ablation (RFA) and photodynamic therapy (PDT) are the main endoscopic locoregional therapies for unresectable eCCA. RFA and PDT could achieve local tumor control and optimize stent patency by inducing tumor necrosis. Currently, RFA and PDT are used increasingly worldwide, and growing evidence tends to support survival benefits.

Clinical question 16: Is endoscopic biliary drainage superior to percutaneous drainage in the management of obstructive eCCA?

Recommendation 16.1: We recommend ERCP for biliary drainage of obstructive distal cholangiocarcinoma (strong recommendation, moderate certainty of evidence).

Recommendation 16.2: Multidisciplinary collaborations could be performed to determine the optimal biliary drainage method (ERCP, PTCD, EUS-biliary drainage) for obstructive hCCA (weak recommendation, low certainty of evidence).

For patients with dCCA, ERCP is the preferred method of biliary drainage.^[167] Compared with PTCD, ERCP has the advantages of less AEs, lower costs, longer survival, less seeding metastasis, and lower recurrence rates.^[189–193] However, the choice remains controversial for patients with hCCA. Incomplete biliary drainage may induce or aggravate infection, potentially hindering tumor resectability. The risk of seeding metastasis by PTCD is also of great concern. Additionally, biliary drainage for hCCA, whether endoscopic or percutaneous, often demands high-level skill and adequate support. Therefore, multidisciplinary collaborations should be performed to choose the optimal method.^[188,194]

A 2016 multicenter retrospective study included 376 patients with resectable dCCA from 30 centers.^[192] With propensity score matching analysis, ERCP had a higher 5-year survival rate and a lower recurrence rate of seeding metastasis compared with PTCD (52.5% *vs.* 34.7%, respectively, $P = 0.017$; 10.7% *vs.* 30.7%, respectively, $P = 0.006$). Three studies reported similar results.^[189–191] A US national cohort study demonstrated that the AE rate with ERCP (8.6%, 640/7445) was lower than that with PTCD (12.3%, 208/1690) for malignant biliary obstruction.^[193] The risk difference was higher for patients with distal *vs.* proximal malignant obstruction. Additionally,

ERCP was associated with shorter hospitalization duration and lower costs *vs.* PTCD.

For patients with hCCA, the choice of biliary drainage method remains controversial. Two RCTs (the DRAINAGE Trial and the INTERCPT Trial) aimed to compare ERCP and PTCD; however, both trials were terminated early because of high mortality with PTCD and unfulfilled enrollment.^[195,196] A 2023 meta-analysis^[197] (17 studies, 2284 patients) reported no significant difference in technical and clinical success rates by preoperative drainage method (PTCD *vs.* ERCP). Comparing the methods, PTCD was associated with fewer AEs, while ERCP was associated with shorter hospitalization duration. For palliative drainage, PTCD demonstrated a higher clinical success rate and less post-drainage cholangitis *vs.* ERCP. Another meta-analysis compared the short- and long-term outcomes with both methods, and found that ERCP and PTCD had similar technical success and 30-day mortality rates, as preoperative drainage methods.^[198] PTCD was associated with lower risks of AEs, method conversion, and pancreatitis *vs.* ERCP. However, long-term, ERCP was associated with a lower risk of seeding metastasis, lower 5-year recurrence rates, and better 5-year OS *vs.* PTCD. A 2019 meta-analysis^[199] (10 studies, 2464 patients) evaluated seeding metastasis and found that ERCP was associated with a much lower risk compared with PTCD (10.5% *vs.* 22.0%, respectively; OR: 0.35, 95% CI: 0.23–0.53). A subgroup analysis yielded the similar results for both hCCA and dCCA (OR: 0.27, 95% CI: 0.13–0.56 and OR: 0.32, 95% CI: 0.17–0.60, respectively). Furthermore, surgeon experience and adequate support should be considered owing to the need for high-risk advanced procedures for hCCA.

Clinical question 17: Could endoscopic RFA and PDT prolong OS in patients with unresectable eCCA?

Recommendation 17: RFA and PDT may be considered alternatives in the palliative treatment of unresectable eCCA, which may provide survival benefits (weak recommendation, moderate certainty of evidence).

Some small RCTs^[200,201] and nearly all meta-analyses^[202–211] showed that RFA and PDT could significantly improve OS and stent patency. Two RCTs failed to obtain positive results, possibly due to different etiologies, number of RFA sessions, and stent type and exchange intervals.^[212,213] With comparable AE rates to those with stenting alone, RFA and PDT are also safe, and cost-effective. As a promising therapeutic option, high-quality studies with large sample sizes are warranted to confirm the roles of these treatments.

A 2022 updated meta-analysis^[207] (19 studies, 1946 patients) showed that compared with stenting alone for unresectable malignant biliary obstruction, RFA had better OS (HR: 0.55, 95% CI: 0.48–0.63; $P < 0.001$), longer survival (standard mean difference: 2.20, 95% CI: 1.17–3.22; $P < 0.001$), and longer stent patency (standard mean difference: 1.37, 95% CI: 0.47–2.26; $P = 0.003$). There were no significant differences in the rates of postoperative abdominal pain, mild bleeding, cholangitis,

and pancreatitis (all $P > 0.05$). Another two meta-analyses confined to patients with eCCA or hCCA obtained similar results.^[203,205] Four RCTs evaluated RFA *vs.* stenting alone,^[200,201,212,213] among which, two RCTs obtained negative results, possibly owing to patient heterogeneity and different protocols (number of RFA sessions, and stent type and exchange intervals).^[200,201] Additionally, RFA is likely to be cost-effective, supported by an incremental cost-effectiveness ratio of £14,392 per quality-adjusted life-years, lower than the threshold of £20,000.^[214]

A 2022 meta-analysis^[204] (55 studies, 2146 patients) showed that PDT was associated with an OS of 11.9 (95% CI: 10.7–13.1) months, which was much better than that for the RFA (8.1 months, 95% CI: 10.7–13.1) and stent-only groups (6.7 months, 95% CI: 4.9–8.4). The stent patency rate was 6.1 (95% CI: 4.2–8) months for PDT, 5.5 (95% CI: 4.2–6.7) months for RFA, and 4.7 (95% CI: 2.6–6.7) months for stenting alone. Two small RCTs,^[215,216] and multiple prospective studies^[217–221] and meta-analyses^[209–211] obtained similar results regarding the survival benefits of PDT. Additionally, combined PDT and chemotherapy could further improve survival without increased AE rates.^[222] However, a concern was the risk of phototoxicity in patients with cholangitis, which occurred at a considerable rate of 23.4% (95% CI: 17.1%–31.3%),^[204] and postoperative adequate drainage should be ensured.

Rehabilitation and supportive treatment

Pain

Pain is experienced by 55% of patients who undergo anticancer treatment and occurs in 66% of patients who have advanced, metastatic, or terminal disease. Chronic cancer-related pain comprises chronic cancer pain caused by the primary cancer or metastases and chronic post-cancer treatment pain caused by anticancer treatment.^[223] Pain management plays an important role in oncologic management. The WHO has developed guidelines for the pharmacologic and radiotherapeutic management of cancer pain in adults and adolescents to provide evidence-based guidance. These guidelines recommend a three-step analgesic ladder for cancer pain management.^[224] Regularly scheduled analgesics could be considered if there is continuous pain. Analgesic regimens may include an opioid, nonsteroidal anti-inflammatory drugs, acetaminophen, and adjuvant analgesics. Moreover, psychosocial support, patient and family education, and multidisciplinary care are important. Interventional therapy can be considered when patients experience inadequate pain management despite pharmacologic therapy, or when patients cannot tolerate an opioid titration program because of AEs.^[225–228]

Nutritional support

Patients with BTC may also have emaciation, indigestion, and fat malabsorption. Research has shown that oral nutritional supplements can improve the nutritional status of patients with BTC.^[229] Given the varying conditions

between patients, an initial individualized nutritional assessment is paramount. The Nutritional Risk Screening tool (NRS-2002) can be used for nutritional risk assessment in hospitalized patients. Concurrent use of the Subjective Global Assessment or Patient-Generated Subjective Global Assessment tool for nutritional assessment is recommended. Furthermore, a patient's nutritional needs may change with treatment progression and disease variability. Continuous monitoring and adjustments to targeted therapy plans when needed are crucial. This requires involvement from a multidisciplinary team that comprises oncologists, dietitians, nurses, and other health experts.

Best supportive care

Supportive care is essential to enhance quality of life and manage symptoms for patients with BTC. Beyond the previously mentioned pain management and nutritional support, several other considerations should be made. First, BTC can result in obstructed bile flow. PTCD or ERCP drainage or stenting are primary interventions.^[230] Additionally, because BTC may affect the liver, regular monitoring and maintenance of liver function are crucial. Some patients might also require calcium and vitamin D supplementation to support bone health. Physical therapy and physical fitness training can be used for rehabilitation, restoring the patient's physical capacity, and enhancing their quality of life. If a patient has compromised immunity, the use of immunomodulators might be considered. It is also noteworthy that individuals with malignant tumors often experience psychological challenges, such as anxiety, sleep disturbance, and depression, which in severe cases can lead to suicidal tendencies. It is essential to closely monitor a patient's mental and emotional well-being, improve family and societal support systems, and seek the assistance of social workers and psychological therapists for guidance.

Follow-up

Currently, there is little direct evidence to support a specific follow-up plan for BTC patients. After radical resection of BTC, the appropriate follow-up schedule must be discussed by a multidisciplinary team comprising patients, surgeons, physicians, pathologists, and other caregivers.

Appendix

Academic Advisors

Yupei Zhao (Peking Union Medical College Hospital), Shuyou Peng (The Second Affiliated Hospital, Zhejiang University), Jia Fan (Zhongshan Hospital, Fudan University), Jiahong Dong (Beijing Tsinghua Changgung Hospital), Zhaoshen Li (Changhai Hospital, Navy Medical University), Zhiwei Quan (Xinhua Hospital, Shanghai Jiaotong University).

Academic Supervisors

Yingbin Liu (Renji Hospital, Shanghai Jiao Tong University School of Medicine), Liwei Wang (Renji

Hospital, Shanghai Jiao Tong University School of Medicine), Enqiang Linghu (The First Medical Center of People's Liberation Army General Hospital), Yexiong Li (Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College).

Expert Committee (in alphabetical order by surname)

Yongrui Bai (Renji Hospital, Shanghai Jiaotong University), Dan Cao (West China Hospital, Sichuan University), Shaochong Zeng (Shanghai Cancer Center, Fudan University), Ningli Chai (The First Medical Center of People's Liberation Army General Hospital), Bo Chen (Cancer Hospital, Chinese Academy of Medical Sciences), Weigang Chen (The First Affiliated Hospital, Shihezi University), Youxiang Chen (The First Affiliated Hospital, Nanchang University), Zhigang Cheng (The Fifth Medical Center of People's Liberation Army General Hospital), Jiujie Cui (Renji Hospital, Shanghai Jiaotong University), Guanghai Dai (The Fifth Medical Center of People's Liberation Army General Hospital), Tong Dang (The Second Affiliated Hospital, Inner Mongolia Medical University), Shisuo Du (Zhongshan Hospital, Fudan University), Feng Duan (The First Medical Center of People's Liberation Army General Hospital), Chihua Fang (Zhujiang Hospital, Southern Medical University), Lu Fang (The Second Affiliated Hospital, Nanchang University), Weijia Fang (The First Affiliated Hospital, Zhejiang University), Feng Fang (Cancer Institute & Hospital, Tianjin Medical University), Zhimin Geng (The First Affiliated Hospital, Xi'an Jiaotong University), Wei Gong (Xinhua Hospital, Shanghai Jiaotong University), Wei Guo (Beijing Friendship Hospital, Capital Medical University), Jianyu Hao (Beijing Chaoyang Hospital, Capital Medical University), Zhaohui He (The Sixth People's Hospital of Zhujiang City), Defei Hong (Sir Run Run Shaw Hospital, Zhejiang University), Bing Hu (The Third Affiliated Hospital, Navy Medical University), Bing Hu (West China Hospital, Sichuan University), Desheng Hu (Hubei Cancer Hospital), Yonghui Huang (Beijing Tsinghua Changgung Hospital), Ming Ji (Beijing Friendship Hospital, Capital Medical University), Haixing Jiang (The First Affiliated Hospital, Guangxi University), Xiaoqing Jiang (The Third Affiliated Hospital, Navy Medical University), Tian'an Jiang (The First Affiliated Hospital, Zhejiang University), Xiang Jin (Tianjin Third Central Hospital), Bing Li (Cancer Hospital, Harbin Medical University), Enxiao Li (The First Affiliated Hospital, Xi'an Jiaotong University), Jiangtao Li (The Second Affiliated Hospital, Zhejiang University), Maolan Li (Renji Hospital, Shanghai Jiao Tong University), Minyang Li (The First Medical Center of People's Liberation Army General Hospital), Qi Li (The First People's Hospital, Shanghai Jiaotong University), Qiang Li (Cancer Institute & Hospital, Tianjin Medical University), Wen Li (Tianjin People's Hospital), Xiangcheng Li (The First Affiliated Hospital, Nanjing Medical University), Xu Li (The First Hospital, Lanzhou University), Yexiong Li (Cancer Hospital, Chinese Academy of Medical Sciences), Yongsheng Li (Renji Hospital, Shanghai Jiao Tong University), Zhiwei Li (Cancer Hospital, Harbin Medical University), Houjie Liang (The Southwest Hospital of AMU), Ping Liang

(The First Medical Center of People's Liberation Army General Hospital), Enqiang Linghu (The First Medical Center of People's Liberation Army General Hospital), Fubao Liu (The First Affiliated Hospital, Anhui Medical University), Houbao Liu (Zhongshan Hospital, Fudan University), Yingbin Liu (Renji Hospital, Shanghai Jiao Tong University), Yufei Lu (Cancer Hospital, Zhengzhou University), Yanglin Pan (Xijing Digest Hospital, Air Force Military University), Songbin Qin (The First Affiliated Hospital, Suzhou University), Jinrong Qiu (The Third Affiliated Hospital, Navy Medical University), Guoliang Shao (Zhejiang Cancer Hospital), Baomin Shi (Xinhua Hospital, Shanghai Jiaotong University), Tianqiang Song (Cancer Institute & Hospital, Tianjin Medical University), Jinjin Sun (Cancer Institute & Hospital, Tianjin Medical University), Jinghua Sun (The Second Affiliated Hospital, Dalian Medical University), Xiaonan Sun (Sir Run Run Shaw Hospital, Zhejiang University), Yongwei Sun (Renji Hospital, Shanghai Jiao Tong University), Zan Teng (The First Affiliated Hospital, China Medical University), Juefeng Wan (Shanghai Cancer Center, Fudan University), Fenghua Wang (Cancer Hospital, Zhongshan University), Liwei Wang (Renji Hospital, Shanghai Jiao Tong University), Qi Wang (The General Hospital, Ningxia Medical University), Weihua Wang (Cancer Hospital, Peking University), Xiaohang Wang (Renji Hospital, Shanghai Jiao Tong University), Xu'an Wang (Renji Hospital, Shanghai Jiao Tong University), Zhenyu Wang (Tianjin Nankai Hospital), Zhongmin Wang (Ruijin Hospital, Shanghai Jiao Tong University), Qiang Xu (Peking Union Medical College Hospital), Maolin Yan (Fujian Provincial Hospital), Liu Yang (Zhejiang Provincial People's Hospital), Jinbo Yue (Shandong Cancer Hospital), Yuansheng Zang (Changzheng Hospital, Navy Medical University), Yaqi Zhai (The First Medical Center of People's Liberation Army General Hospital), Guoliang Zhang (Tianjin First Central Hospital), Huojun Zhang (Changhai Hospital, Navy Medical University), Tong Zhang (The Affiliated Hospital, Inner Mongolia Medical University), Xiaofeng Zhang (The First People's Hospital of Hangzhou), Enhao Zhao (Renji Hospital, Shanghai Jiao Tong University), Qiyu Zhao (The First Affiliated Hospital, Zhejiang University), Fazhao Zhi (Nanfeng Hospital, Southern Medical University), Qiuzi Zhong (Beijing Hospital), Jun Zhou (Cancer Hospital, Peking University), Yuhong Zhou (Zhongshan Hospital, Fudan University)

Methodology Group

Shiyao Chen (Zhongshan Hospital, Fudan University), Xuejuan Jin (Zhongshan Hospital, Fudan University), Xiaoqing Zeng (Zhongshan Hospital, Fudan University)

Academic Secretary

Jiujie Cui (Renji Hospital, Shanghai Jiao Tong University School of Medicine), Yaqi Zhai (The First Medical Center of People's Liberation Army General Hospital), Xiaohang Wang (Renji Hospital, Shanghai Jiao Tong University School of Medicine), Yongsheng Li (Renji Hospital, Shanghai Jiao Tong University School of Medicine).

Conflicts of interest

None.

References

- Xia C, Dong X, Li H, Cao M, Sun D, He S, *et al.* Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chin Med J* 2022;135:584–590. doi: 10.1097/CM9.0000000000002108.
- Organization WH. WHO handbook for guideline development, 2nd Edition. 2014. Available from: <https://www.who.int/publications/i/item/9789241548960>.
- Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, *et al.* GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ* 2016;353:i2089. doi: 10.1136/bmj.i2089.
- Brouwers MC, Kerkvliet K, Spithoff K. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. *BMJ* 2016;352:i1152. doi: 10.1136/bmj.i1152.
- Chen Y, Yang K, Marušić A, Qaseem A, Meerpohl JJ, Flottorp S, *et al.* A reporting tool for practice guidelines in health care: the RIGHT statement. *Z Evid Fortbild Qual Gesundheitswes* 2017;127:128–30. doi: 10.1016/j.zefq.2017.10.008.
- Yao X, Ma J, Wang Q, Kanters D, Ali MU, Florez ID. A Comparison of AGREE and RIGHT: which Clinical Practice Guideline Reporting Checklist Should Be Followed by Guideline Developers? *J Gen Intern Med* 2020;35:894–898. doi: 10.1007/s11606-019-05508-3.
- Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, *et al.* AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010;182:E839–842. doi: 10.1503/cmaj.090449.
- Chen Y, Yang K, Marušić A, Qaseem A, Meerpohl JJ, Flottorp S, *et al.* A Reporting Tool for Practice Guidelines in Health Care: The RIGHT Statement. *Ann Intern Med* 2017;166:128–132. doi: 10.7326/m16-1565.
- Qiu SM, Liu FT, Wu WW, Liu YB. Progress of genomic mutation spectrum in biliary tract malignant tumors (in Chinese). *Chin J Surg* 2023;61:1124–1129. doi: 10.3760/cma.j.cn112139-20230518-00208.
- Liu LG, Zhang YJ, Wang XA, Liu YB. Advance in immunotherapy on biliary tract cancers (in Chinese). *Chin J Surg* 2021;59:156–160. doi: 10.3760/cma.j.cn112139-20200515-00382.
- Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: Epidemiology and risk factors. *Liver Int* 2019;39 Suppl 1:19–31. doi: 10.1111/liv.14095.
- Petrick JL, Thistle JE, Zeleniuch-Jacquotte A, Zhang X, Wactawski-Wende J, Van Dyke AL, *et al.* Body Mass Index, Diabetes and Intrahepatic Cholangiocarcinoma Risk: The Liver Cancer Pooling Project and Meta-analysis. *Am J Gastroenterol* 2018;113:1494–1505. doi: 10.1038/s41395-018-0207-4.
- Clements O, Eliahoo J, Kim JU, Taylor-Robinson SD, Khan SA. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: A systematic review and meta-analysis. *J Hepatol* 2020;72:95–103. doi: 10.1016/j.jhep.2019.09.007.
- Sithithaworn P, Yongvanit P, Duenngai K, Kiatsopit N, Pairojkl C. Roles of liver fluke infection as risk factor for cholangiocarcinoma. *J Hepatobiliary Pancreat Sci* 2014;21:301–308. doi: 10.1002/jhbp.62.
- Petrick JL, McMenamin Ú C, Zhang X, Zeleniuch-Jacquotte A, Wactawski-Wende J, Simon TG, *et al.* Exogenous hormone use, reproductive factors and risk of intrahepatic cholangiocarcinoma among women: results from cohort studies in the Liver Cancer Pooling Project and the UK Biobank. *Br J Cancer* 2020;123:316–324. doi: 10.1038/s41416-020-0835-5.
- Palmer WC, Patel T. Are common factors involved in the pathogenesis of primary liver cancers? A meta-analysis of risk factors for intrahepatic cholangiocarcinoma. *J Hepatol* 2012;57:69–76. doi: 10.1016/j.jhep.2012.02.022.
- Ren T, Li YS, Geng YJ, Li ML, Wu XS, Wu WW, *et al.* Analysis of treatment modalities and prognosis of patients with gallbladder cancer in China from 2010 to 2017 (in Chinese). *Chin J Surg* 2020;58:697–706. doi: 10.3760/cma.j.cn112139-20200403-00279.
- Hsing AW, Bai Y, Andreotti G, Rashid A, Deng J, Chen J, *et al.* Family history of gallstones and the risk of biliary tract cancer

- and gallstones: a population-based study in Shanghai, China. *Int J Cancer* 2007;121:832–838. doi: 10.1002/ijc.22756.
19. Geng Y, Chen S, Yang Y, Miao H, Li X, Li G, *et al.* Long-term exposure to genistein inhibits the proliferation of gallbladder cancer by downregulating the MCM complex. *Sci Bull (Beijing)* 2022;67:813–824. doi: 10.1016/j.scib.2022.01.011.
 20. Lewis JT, Talwalkar JA, Rosen CB, Smyrk TC, Abraham SC. Prevalence and risk factors for gallbladder neoplasia in patients with primary sclerosing cholangitis: evidence for a metaplasia-dysplasia-carcinoma sequence. *Am J Surg Pathol* 2007;31:907–913. doi: 10.1097/01.pas.0000213435.99492.8a.
 21. Koshiol J, Wozniak A, Cook P, Adaniel C, Acevedo J, Azócar L, *et al.* *Salmonella enterica* serovar Typhi and gallbladder cancer: a case-control study and meta-analysis. *Cancer Med* 2016;5:3310–3235. doi: 10.1002/cam4.915.
 22. Kamisawa T, Kaneko K, Itoi T, Ando H. Pancreaticobiliary maljunction and congenital biliary dilatation. *Lancet Gastroenterol Hepatol* 2017;2:610–618. doi: 10.1016/s2468-1253(17)30002-x.
 23. Li ZM, Wu ZX, Han B, Mao YQ, Chen HL, Han SF, *et al.* The association between BMI and gallbladder cancer risk: a meta-analysis. *Oncotarget* 2016;7:43669–43679. doi: 10.18632/oncotarget.9664.
 24. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209–249. doi: 10.3322/caac.21660.
 25. Banales JM, Marin JJG, Lamarca A, Rodrigues PM, Khan SA, Roberts LR, *et al.* Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol* 2020;17:557–588. doi: 10.1038/s41575-020-0310-z.
 26. Shin HR, Oh JK, Masuyer E, Curado MP, Bouvard V, Fang Y, *et al.* Comparison of incidence of intrahepatic and extrahepatic cholangiocarcinoma—focus on East and South-Eastern Asia. *Asian Pac J Cancer Prev* 2010;11:1159–1166.
 27. Banales JM, Cardinale V, Carpino G, Marziani M, Andersen JB, Invernizzi P, *et al.* Expert consensus document: Cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). *Nat Rev Gastroenterol Hepatol* 2016;13:261–280. doi: 10.1038/nrgastro.2016.51.
 28. Khuntikeo N, Chamadol N, Yongvanit P, Loilome W, Namwat N, Sithithaworn P, *et al.* Cohort profile: cholangiocarcinoma screening and care program (CASCAP). *BMC Cancer* 2015;15:459. doi: 10.1186/s12885-015-1475-7.
 29. Patel T. Worldwide trends in mortality from biliary tract malignancies. *BMC Cancer* 2002;2:10. doi: 10.1186/1471-2407-2-10.
 30. Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-Year Trends in Cholangiocarcinoma Incidence in the U.S.: Intrahepatic Disease on the Rise. *Oncologist* 2016;21:594–599. doi: 10.1634/theoncologist.2015-0446.
 31. Zatonski WA, Lowenfels AB, Boyle P, Maisonneuve P, Bueno de Mesquita HB, Ghadirian P, *et al.* Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH Program of the International Agency for Research on Cancer. *J Natl Cancer Inst* 1997;89:1132–1138. doi: 10.1093/jnci/89.15.1132.
 32. Wang Z, Wang S, Jia Z, Hu Y, Cao D, Yang M, *et al.* YKL-40 derived from infiltrating macrophages cooperates with GDF15 to establish an immune suppressive microenvironment in gallbladder cancer. *Cancer Lett* 2023;563:216184. doi: 10.1016/j.canlet.2023.216184.
 33. Li Y, Yang B, Miao H, Liu L, Wang Z, Jiang C, *et al.* Nicotinamide N-methyltransferase promotes M2 macrophage polarization by IL6 and MDSC conversion by GM-CSF in gallbladder carcinoma. *Hepatology* 2023;78:1352–1367. doi: 10.1097/hep.0000000000000028.
 34. Liu L, Li Y, Cao D, Qiu S, Li Y, Jiang C, *et al.* SIRT3 inhibits gallbladder cancer by induction of AKT-dependent ferroptosis and blockade of epithelial-mesenchymal transition. *Cancer Lett* 2021;510:93–104. doi: 10.1016/j.canlet.2021.04.007.
 35. Li G, Pu P, Pan M, Weng X, Qiu S, Li Y, *et al.* Topological reorganization and functional alteration of distinct genomic components in gallbladder cancer. *Front Med* 2024;18:109–127. doi: 10.1007/s11684-023-1008-8.
 36. Li M, Liu F, Zhang F, Zhou W, Jiang X, Yang Y, *et al.* Genomic ERBB2/ERBB3 mutations promote PD-L1-mediated immune escape in gallbladder cancer: a whole-exome sequencing analysis. *Gut* 2019;68:1024–1033. doi: 10.1136/gutjnl-2018-316039.
 37. Li M, Zhang Z, Li X, Ye J, Wu X, Tan Z, *et al.* Whole-exome and targeted gene sequencing of gallbladder carcinoma identifies recurrent mutations in the ErbB pathway. *Nat Genet* 2014;46:872–876. doi: 10.1038/ng.3030.
 38. Lamarca A, Barriuso J, Chander A, McNamara MG, Hubner RA, O'Reilly D, *et al.* (18)F-fluorodeoxyglucose positron emission tomography ((18)FDG-PET) for patients with biliary tract cancer: Systematic review and meta-analysis. *J Hepatol* 2019;71:115–129. doi: 10.1016/j.jhep.2019.01.038.
 39. Liu YB, Chen W. Attach importance to the standardized diagnosis and treatment of gallbladder carcinoma (in Chinese). *Chin J Surg* 2021;59:249–254. doi: 10.3760/cma.j.cn112139-20210115-00031.
 40. Angsuwatcharakon P, Kulpatcharapong S, Moon JH, Ramchandani M, Lau J, Isayama H, *et al.* Consensus guidelines on the role of cholangioscopy to diagnose indeterminate biliary stricture. *HPB (Oxford)* 2022;24:17–29. doi: 10.1016/j.hpb.2021.05.005.
 41. Kulpatcharapong S, Pittayanon R, Kerr SJ, Rerknimitr R. Diagnostic performance of digital and video cholangioscopes in patients with suspected malignant biliary strictures: a systematic review and meta-analysis. *Surg Endosc* 2022;36:2827–2841. doi: 10.1007/s00464-021-08571-2.
 42. Gerges C, Beyna T, Tang RSY, Bahin F, Lau JYW, van Geenen E, *et al.* Digital single-operator peroral cholangioscopy-guided biopsy sampling versus ERCP-guided brushing for indeterminate biliary strictures: a prospective, randomized, multicenter trial (with video). *Gastrointest Endosc* 2020;91:1105–1113. doi: 10.1016/j.gie.2019.11.025.
 43. Han S, Tatman P, Mehrotra S, Wani S, Attwell AR, Edmundowicz SA, *et al.* Combination of ERCP-Based Modalities Increases Diagnostic Yield for Biliary Strictures. *Dig Dis Sci* 2021;66:1276–1284. doi: 10.1007/s10620-020-06335-x.
 44. Draganov PV, Chauhan S, Wagh MS, Gupte AR, Lin T, Hou W, *et al.* Diagnostic accuracy of conventional and cholangioscopy-guided sampling of indeterminate biliary lesions at the time of ERCP: a prospective, long-term follow-up study. *Gastrointest Endosc* 2012;75:347–353. doi: 10.1016/j.gie.2011.09.020.
 45. Fukuda Y, Tsuyuguchi T, Sakai Y, Tsuchiya S, Saisyo H. Diagnostic utility of peroral cholangioscopy for various bile-duct lesions. *Gastrointest Endosc* 2005;62:374–382. doi: 10.1016/j.gie.2005.04.032.
 46. Kokoy-Mondragon C, Brooks C, Amin S, Desai AP, Poneris JM, Sethi A, *et al.* Comparison of Accuracy of Simultaneous Cholangioscopic Biopsies and Fluorescence in-Situ Hybridization in Biliary Strictures. *Gastroenterology* 2017;152:S297–S298. doi: 10.1016/S0016-5085(17)31282-9.
 47. Fujii-Lau LL, Thosani NC, Al-Haddad M, Acoba J, Wray CJ, Zavanjanja R, *et al.* American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in the diagnosis of malignancy in biliary strictures of undetermined etiology: summary and recommendations. *Gastrointest Endosc* 2023;98:685–693. doi: 10.1016/j.gie.2023.06.005.
 48. Kulpatcharapong S, Pittayanon R, S JK, Rerknimitr R. Diagnostic performance of different cholangioscopes in patients with biliary strictures: a systematic review. *Endoscopy* 2020;52:174–185. doi: 10.1055/a-1083-6105.
 49. Fugazza A, Gabbiadini R, Tringali A, De Angelis CG, Mosca P, Maurano A, *et al.* Digital single-operator cholangioscopy in diagnostic and therapeutic bilio-pancreatic diseases: A prospective, multicenter study. *Dig Liver Dis* 2022;54:1243–1249. doi: 10.1016/j.dld.2022.04.019.
 50. Njei B, McCarty TR, Varadarajulu S, Navaneethan U. Cost utility of ERCP-based modalities for the diagnosis of cholangiocarcinoma in primary sclerosing cholangitis. *Gastrointest Endosc* 2017;85:773–781.e710. doi: 10.1016/j.gie.2016.08.020.
 51. Ramchandani M, Reddy DN, Lakhtakia S, Tandan M, Maydeo A, Chandrashekar TS, *et al.* Per oral cholangiopancreatography in pancreatic biliary diseases—expert consensus statements. *World J Gastroenterol* 2015;21:4722–4734. doi: 10.3748/wjg.v21.i15.4722.
 52. Sun B, Moon JH, Cai Q, Rerknimitr R, Ma S, Lakhtakia S, *et al.* Review article: Asia-Pacific consensus recommendations on endoscopic tissue acquisition for biliary strictures. *Aliment Pharmacol Ther* 2018;48:138–151. doi: 10.1111/apt.14811.
 53. Pouw RE, Barret M, Biermann K, Bisschops R, Czakó L, Gecse KB, *et al.* Endoscopic tissue sampling - Part 1: Upper gastroin-

- testinal and hepatopancreatobiliary tracts. European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2021;53:1174–1188. doi: 10.1055/a-1611-5091.
54. Chinese guidelines for ERCP (2018) (in Chinese). *Chin J Intern Med* 2018;57:772–801. doi: 10.3760/cma.j.issn.0578-1426.2018.11.002.
 55. Chiang A, Theriault M, Salim M, James PD. The incremental benefit of EUS for the identification of malignancy in indeterminate extrahepatic biliary strictures: A systematic review and meta-analysis. *Endosc Ultrasound* 2019;8:310–317. doi: 10.4103/eus.eus.24_19.
 56. Yoon SB, Moon SH, Ko SW, Lim H, Kang HS, Kim JH. Brush Cytology, Forceps Biopsy, or Endoscopic Ultrasound-Guided Sampling for Diagnosis of Bile Duct Cancer: A Meta-Analysis. *Dig Dis Sci* 2022;67:3284–3297. doi: 10.1007/s10620-021-07138-4.
 57. Lee YN, Moon JH, Choi HJ, Kim HK, Lee HW, Lee TH, *et al.* Tissue acquisition for diagnosis of biliary strictures using peroral cholangioscopy or endoscopic ultrasound-guided fine-needle aspiration. *Endoscopy* 2019;51:50–59. doi: 10.1055/a-0645-1395.
 58. Lee YN, Moon JH, Choi HJ, Kim HK, Choi SY, Choi MH, *et al.* Diagnostic approach using ERCP-guided transpapillary forceps biopsy or EUS-guided fine-needle aspiration biopsy according to the nature of stricture segment for patients with suspected malignant biliary stricture. *Cancer Med* 2017;6:582–590. doi: 10.1002/cam4.1034.
 59. Malikowski T, Levy MJ, Gleeson FC, Storm AC, Vargas EJ, Topazian MD, *et al.* Endoscopic Ultrasound/Fine Needle Aspiration Is Effective for Lymph Node Staging in Patients With Cholangiocarcinoma. *Hepatology* 2020;72:940–948. doi: 10.1002/hep.31077.
 60. de Jong DM, van de Vondervoort S, Dwarkasing RS, Doukas M, Voermans RP, Verdonk RC, *et al.* Endoscopic ultrasound in patients with resectable perihilar cholangiocarcinoma: impact on clinical decision-making. *Endosc Int Open* 2023;11:E162–e168. doi: 10.1055/a-2005-3679.
 61. Vogel A, Bridgewater J, Edeline J, Kelley RK, Klumpen HJ, Malka D, *et al.* Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023;34:127–140. doi: 10.1016/j.annonc.2022.10.506.
 62. Dumonceau JM, Deprez PH, Jenssen C, Iglesias-Garcia J, Larghi A, Vanbiervliet G, *et al.* Indications, results, and clinical impact of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline - Updated January 2017. *Endoscopy* 2017;49:695–714. doi: 10.1055/s-0043-109021.
 63. Barr Fritcher EG, Voss JS, Brankley SM, Campion MB, Jenkins SM, Keeney ME, *et al.* An Optimized Set of Fluorescence In Situ Hybridization Probes for Detection of Pancreatobiliary Tract Cancer in Cytology Brush Samples. *Gastroenterology* 2015;149:1813–1824. e1811. doi: 10.1053/j.gastro.2015.08.046.
 64. Arai Y, Totoki Y, Hosoda F, Shiota T, Hama N, Nakamura H, *et al.* Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. *Hepatology* 2014;59:1427–1434. doi: 10.1002/hep.26890.
 65. Goyal L, Govindan A, Sheth RA, Nardi V, Blazzkowsky LS, Faris JE, *et al.* Prognosis and Clinicopathologic Features of Patients With Advanced Stage Isocitrate Dehydrogenase (IDH) Mutant and IDH Wild-Type Intrahepatic Cholangiocarcinoma. *Oncologist* 2015;20:1019–1027. doi: 10.1634/theoncologist.2015.0210.
 66. Wang P, Dong Q, Zhang C, Kuan PF, Liu Y, Jeck WR, *et al.* Mutations in isocitrate dehydrogenase 1 and 2 occur frequently in intrahepatic cholangiocarcinomas and share hypermethylation targets with glioblastomas. *Oncogene* 2013;32:3091–3100. doi: 10.1038/onc.2012.315.
 67. Yang M, Li WW, Chen JH, Cui MH, Liu JL. The value of caudate lobectomy in hilar cholangiocarcinoma treatment A meta-analysis. *Medicine* 2021;100:9. doi: 10.1097/md.00000000000024727.
 68. Birgin E, Rasbach E, Reissfelder C, Rahbari NN. A systematic review and meta-analysis of caudate lobectomy for treatment of hilar cholangiocarcinoma. *EJSO* 2020;46:747–753. doi: 10.1016/j.ejso.2020.01.023.
 69. Gilbert RWD, Lenet T, Cleary SP, Smoot R, Tzeng CWD, Rocha FG, *et al.* Does Caudate Resection Improve Outcomes of Patients Undergoing Curative Resection for Perihilar Cholangiocarcinoma? A Systematic Review and Meta-Analysis. *Ann Surg Oncol* 2022;29:6759–6771. doi: 10.1245/s10434-022-11990-7.
 70. Li FY, Jiang Y, Jiang LY, Li QB, Yan XY, Huang SH, *et al.* Effect of lymph node resection on prognosis of resectable intrahepatic cholangiocarcinoma: A systematic review and meta-analysis. *Front Oncol* 2022;12:8. doi: 10.3389/fonc.2022.957792.
 71. Amini N, Ejaz A, Spolverato G, Maithel SK, Kim Y, Pawlik TM. Management of Lymph Nodes During Resection of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma: A Systematic Review. *J Gastrointest Surg* 2014;18:2136–2148. doi: 10.1007/s11605-014-2667-1.
 72. Zeng Y, Li Y, Zhang X. Effect of abdominal lymphadenectomy on prognosis of intrahepatic cholangiocarcinoma: a systematic review and Meta analysis (in Chinese). *Chin J Digest Surg* 2016;15:339–345.
 73. Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and Prognosis for Patients With Intrahepatic Cholangiocarcinoma Systematic Review and Meta-analysis. *JAMA Surg* 2014;149:565–574. doi: 10.1001/jamasurg.2013.5137.
 74. Zhou R, Lu DH, Li WD, Tan WL, Zhu SC, Chen XQ, *et al.* Is lymph node dissection necessary for resectable intrahepatic cholangiocarcinoma? A systematic review and meta-analysis. *HPB* 2019;21:784–792. doi: 10.1016/j.hpb.2018.12.011.
 75. Ren T, Li YS, Dang XY, Li Y, Shao ZY, Bao RF, *et al.* Prognostic significance of regional lymphadenectomy in T1b gallbladder cancer: Results from 24 hospitals in China. *World J Gastrointest Surg* 2021;13:176–186. doi: 10.4240/wjgs.v13.i2.176.
 76. Wu XS, Zhu YD, Jin YP, Li ML, Gong W, Liu YB. Diagnosis and treatment for unexpected gallbladder carcinoma (a retrospective study of 45 cases) (in Chinese). *Chin J Surg* 2019;57:265–270. doi: 10.3760/cma.j.issn.0529-5815.2019.04.005.
 77. Balakrishnan A, Barmounakis P, Demiris N, Jah A, Spiers HVM, Talukder S, *et al.* Surgical outcomes of gallbladder cancer: the OMEGA retrospective, multicentre, international cohort study. *Eclinicalmedicine* 2023;59:11. doi: 10.1016/j.eclinm.2023.101951.
 78. Kwon W, Kim H, Han Y, Hwang YJ, Kim SG, Kwon HJ, *et al.* Role of tumour location and surgical extent on prognosis in T2 gallbladder cancer: an international multicentre study. *Br J Surg* 2020;107:1334–1343. doi: 10.1002/bjs.11618.
 79. Chen MY, Cao JS, Xiang YK, Ma XC, Bai Y, Lai QH, *et al.* Hepatectomy strategy for T2 gallbladder cancer between segment IVb and V resection and wedge resection: A propensity score-matched. *Surgery* 2021;169:1304–1311. doi: 10.1016/j.surg.2020.12.039.
 80. Wang ZC, Liu HL, Huang Y, Wang J, Li JJ, Liu LP, *et al.* Comparative analysis of postoperative curative effect of liver wedge resection and liver IVb. *Front Surg* 2023;10:7. doi: 10.3389/fsurg.2023.1139947.
 81. Horiguchi A, Miyakawa S, Ishihara S, Miyazaki M, Ohtsuka M, Shimizu H, *et al.* Gallbladder bed resection or hepatectomy of segments 4a and 5 for pT2 gallbladder carcinoma: analysis of Japanese registration cases by the study group for biliary surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepatobiliary Pancreat Sci* 2013;20:518–524. doi: 10.1007/s00534-012-0584-9.
 82. Matsui S, Tanioka T, Nakajima K, Saito T, Kato S, Tomii C, *et al.* Surgical and Oncological Outcomes of Wedge Resection Versus Segment 4b+5 Resection for T2 and T3 Gallbladder Cancer: a Meta-Analysis. *J Gastrointest Surg* 2023;27:1954–1962. doi: 10.1007/s11605-023-05698-6.
 83. Quinn LM, Mann K, Jones RP, Bathla S, Stremitzer S, Dunne DF, *et al.* Defining enhanced recovery after resection of peri-hilar cholangiocarcinoma. *Eur J Surg Oncol* 2019;45:1439–1445. doi: 10.1016/j.ejso.2019.03.033.
 84. Shao Y, Aji T, Ran B, Jiang T, Wen H. Efficacy analysis of using enhanced recovery after surgery in perioperative period of radical surgery for cholangiocarcinoma. *HPB* 2018;20:S407.
 85. Bond-Smith G, Belgaumkar AP, Davidson BR, Gurusamy KS. Enhanced recovery protocols for major upper gastrointestinal, liver and pancreatic surgery. *Cochrane Database Syst Rev* 2016;2:CD011382. doi: 10.1002/14651858.CD011382.pub2.
 86. Moole H, Bechtold M, Puli SR. Efficacy of preoperative biliary drainage in malignant obstructive jaundice: a meta-analysis and systematic review. *World J Surg Oncol* 2016;14:182. doi: 10.1186/s12957-016-0933-2.
 87. Nimura Y. Preoperative biliary drainage before resection for cholangiocarcinoma (Pro). *HPB* 2008;10.
 88. Wang Q, Gurusamy KS, Lin H, Xie X, Wang C. Pre-operative biliary drainage for obstructive jaundice. *Cochrane database of systematic reviews (Online)* 2012;3:CD005444.
 89. Cherqui D, Benoist S, Malassagne B, Humeres R, Rodriguez V, Fagniez PL. Major liver resection for carcinoma in jaundiced patients

- without preoperative biliary drainage. *Arch Surg* 2000;135:302–308. doi: 10.1001/archsurg.135.3.302.
90. Celotti A, Solaini L, Montori G, Coccolini F, Tognali D, Baiocchi G. Preoperative biliary drainage in hilar cholangiocarcinoma: Systematic review and meta-analysis. *Eur J Surg Oncol* 2017;43:1628–1635. doi: 10.1016/j.ejso.2017.04.001.
 91. Song X, Hu Y, Li Y, Shao R, Liu F, Liu Y. Overview of current targeted therapy in gallbladder cancer. *Signal Transduct Target Ther* 2020; 5: 230. doi: 10.1038/s41392-020-00324-2.
 92. Matsuyama R, Mori R, Ota Y, Homma Y, Yabusita Y, Hiratani S, *et al.* Impact of Gemcitabine Plus S1 Neoadjuvant Chemotherapy on Borderline Resectable Perihilar Cholangiocarcinoma. *Ann Surg Oncol* 2022;29:2393–2405. doi: 10.1245/s10434-021-11206-4.
 93. Kobayashi S, Tomokuni A, Gotoh K, Takahashi H, Akita H, Marubashi S, *et al.* Evaluation of the safety and pathological effects of neoadjuvant full-dose gemcitabine combination radiation therapy in patients with biliary tract cancer. *Cancer Chemother Pharmacol* 2015;76:1191–1198. doi: 10.1007/s00280-015-2908-3.
 94. Sumiyoshi T, Shima Y, Okabayashi T, Negoro Y, Shimada Y, Iwata J, *et al.* Chemoradiotherapy for Initially Unresectable Locally Advanced Cholangiocarcinoma. *World J Surg* 2018;42:2910–2918. doi: 10.1007/s00268-018-4558-1.
 95. Engineer R, Goel M, Chopra S, Patil P, Purandare N, Rangarajan V, *et al.* Neoadjuvant Chemoradiation Followed by Surgery for Locally Advanced Gallbladder Cancers: A New Paradigm. *Ann Surg Oncol* 2016;23:3009–3015. doi: 10.1245/s10434-016-5197-0.
 96. Sutton TL, Billingsley KG, Walker BS, Enestvedt CK, Dewey EN, Orloff SL, *et al.* Neoadjuvant chemotherapy is associated with improved survival in patients undergoing hepatic resection for intrahepatic cholangiocarcinoma. *Am J Surg* 2021;221:1182–1187. doi: 10.1016/j.amjsurg.2021.02.029.
 97. Le Roy B, Gelli M, Pittau G, Allard MA, Pereira B, Serji B, *et al.* Neoadjuvant chemotherapy for initially unresectable intrahepatic cholangiocarcinoma. *Br J Surg* 2018;105:839–847. doi: 10.1002/bjs.10641.
 98. Creasy JM, Goldman DA, Dudeja V, Lowery MA, Cercek A, Balachandran VP, *et al.* Systemic Chemotherapy Combined with Resection for Locally Advanced Gallbladder Carcinoma: Surgical and Survival Outcomes. *J Am Coll Surg* 2017;224:906–916. doi: 10.1016/j.jamcollsurg.2016.12.058.
 99. Chaudhari VA, Ostwal V, Parkar S, Sahu A, Toshniwal A, Ramaswamy A, *et al.* Outcome of neoadjuvant chemotherapy in “locally advanced/borderline resectable” gallbladder cancer: the need to define indications. *HPB (Oxford)* 2018;20:841–847. doi: 10.1016/j.hpb.2018.03.008.
 100. Yang Z, Jiang X. Efficacy and safety comparison of neoadjuvant chemotherapy followed by surgery and upfront surgery for treating intrahepatic cholangiocarcinoma: a systematic review and meta-analysis. *BMC Gastroenterol* 2023;23:122. doi: 10.1186/s12876-023-02754-y.
 101. Hakeem AR, Papoulas M, Menon KV. The role of neoadjuvant chemotherapy or chemoradiotherapy for advanced gallbladder cancer - A systematic review. *Eur J Surg Oncol* 2019;45:83–91. doi: 10.1016/j.ejso.2018.08.020.
 102. Primrose JN, Fox RP, Palmer DH, Malik HZ, Prasad R, Mirza D, *et al.* Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. *Lancet Oncol* 2019;20:663–673. doi: 10.1016/s1470-2045(18)30915-x.
 103. Nakachi K, Ikeda M, Konishi M, Nomura S, Katayama H, Kataoka T, *et al.* Adjuvant S-1 compared with observation in resected biliary tract cancer (JCOG1202, ASCOT): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet* 2023;401:195–203. doi: 10.1016/s0140-6736(22)02038-4.
 104. Edeline J, Benabdelghani M, Bertalet A, Watelet J, Hammel P, Joly JP, *et al.* Gemcitabine and Oxaliplatin Chemotherapy or Surveillance in Resected Biliary Tract Cancer (PRODIGE 12-ACCORD 18-UNICANCER GI): A Randomized Phase III Study. *J Clin Oncol* 2019;37:658–667. doi: 10.1200/jco.18.00050.
 105. Ebata T, Hirano S, Konishi M, Uesaka K, Tsuchiya Y, Ohtsuka M, *et al.* Randomized clinical trial of adjuvant gemcitabine chemotherapy versus observation in resected bile duct cancer. *Br J Surg* 2018;105:192–202. doi: 10.1002/bjs.10776.
 106. Takada T, Amano H, Yasuda H, Nimura Y, Matsushiro T, Kato H, *et al.* Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. *Cancer* 2002;95:1685–1695. doi: 10.1002/cncr.10831.
 107. Neoptolemos JP, Moore MJ, Cox TF, Valle JW, Palmer DH, McDonald AC, *et al.* Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. *JAMA* 2012;308:147–156. doi: 10.1001/jama.2012.7352.
 108. Kobayashi S, Nagano H, Tomokuni A, Gotoh K, Sakai D, Hatano E, *et al.* A Prospective, Randomized Phase II Study of Adjuvant Gemcitabine Versus S-1 After Major Hepatectomy for Biliary Tract Cancer (KHBO 1208): Kansai Hepato-Biliary Oncology Group. *Ann Surg* 2019;270:230–237. doi: 10.1097/sla.0000000000002865.
 109. Seita K, Ebata T, Mizuno T, Maeda A, Yamaguchi R, Kurumiya Y, *et al.* Phase 2 Trial of Adjuvant Chemotherapy With S-1 for Node-Positive Biliary Tract Cancer (N-SOG 09). *Ann Surg Oncol* 2020;27:2348–2356. doi: 10.1245/s10434-020-08355-3.
 110. Ben-Josef E, Guthrie KA, El-Khoueiry AB, Corless CL, Zalupski MM, Lowy AM, *et al.* SWOG S0809: A Phase II Intergroup Trial of Adjuvant Capecitabine and Gemcitabine Followed by Radiotherapy and Concurrent Capecitabine in Extrahepatic Cholangiocarcinoma and Gallbladder Carcinoma. *J Clin Oncol* 2015;33:2617–2622. doi: 10.1200/jco.2014.60.2219.
 111. Siebenhüner AR, Seifert H, Bachmann H, Seifert B, Winder T, Feilchenfeldt J, *et al.* Adjuvant treatment of resectable biliary tract cancer with cisplatin plus gemcitabine: A prospective single center phase II study. *BMC Cancer* 2018;18:72. doi: 10.1186/s12885-017-3967-0.
 112. Shimizu K, Kotera Y, Aruga A, Takeshita N, Takasaki K, Yamamoto M. Clinical utilization of postoperative dendritic cell vaccine plus activated T-cell transfer in patients with intrahepatic cholangiocarcinoma. *J Hepatobiliary Pancreat Sci* 2012;19:171–178. doi: 10.1007/s00534-011-0437-y.
 113. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, *et al.* Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010;362:1273–1281. doi: 10.1056/NEJMoa0908721.
 114. Morizane C, Okusaka T, Mizusawa J, Katayama H, Ueno M, Ikeda M, *et al.* Combination gemcitabine plus S-1 versus gemcitabine plus cisplatin for advanced/recurrent biliary tract cancer: the FUGA-BT (JCOG1113) randomized phase III clinical trial. *Ann Oncol* 2019;30:1950–1958. doi: 10.1093/annonc/mdz402.
 115. Kim ST, Kang JH, Lee J, Lee HW, Oh SY, Jang JS, *et al.* Capecitabine plus oxaliplatin versus gemcitabine plus oxaliplatin as first-line therapy for advanced biliary tract cancers: a multicenter, open-label, randomized, phase III, noninferiority trial. *Ann Oncol* 2019;30:788–795. doi: 10.1093/annonc/mdz058.
 116. Ioka T, Kanai M, Kobayashi S, Sakai D, Eguchi H, Baba H, *et al.* Randomized phase III study of gemcitabine, cisplatin plus S-1 versus gemcitabine, cisplatin for advanced biliary tract cancer (KHBO1401- MITSUBA). *J Hepatobiliary Pancreat Sci* 2023;30:102–110. doi: 10.1002/jhbp.1219.
 117. Oh D-Y, He AR, Qin S, Chen L-T, Okusaka T, Vogel A, *et al.* Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. *NEJM Evidence* 2022;1:EVIDoa2200015. doi: 10.1056/EVIDoa2200015.
 118. Kelley RK, Ueno M, Yoo C, Finn RS, Furuse J, Ren Z, *et al.* Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2023;401:1853–1865. doi: 10.1016/s0140-6736(23)00727-4.
 119. Cui XY, Li XC, Cui JJ, Wu XS, Zou L, Song XL, *et al.* Modified FOLFIRINOX for unresectable locally advanced or metastatic gallbladder cancer, a comparison with GEMOX regimen. *Hepatobiliary Surg Nutr* 2021;10:498–506. doi: 10.21037/hbsn-20-846.
 120. Zou L, Li X, Wu X, Cui J, Cui X, Song X, *et al.* Modified FOLFIRINOX versus gemcitabine plus oxaliplatin as first-line chemotherapy for patients with locally advanced or metastatic cholangiocarcinoma: a retrospective comparative study. *BMC Cancer* 2021;21:818. doi: 10.1186/s12885-021-08549-2.
 121. Sahai V, Catalano PJ, Zalupski MM, Lubner SJ, Menge MR, Nimeiri HS, *et al.* Nab-Paclitaxel and Gemcitabine as First-line Treatment of Advanced or Metastatic Cholangiocarcinoma: A Phase 2 Clinical Trial. *JAMA Oncol* 2018;4:1707–1712. doi: 10.1001/jamaoncol.2018.3277.

122. Oh DY, Lee KH, Lee DW, Yoon J, Kim TY, Bang JH, *et al.* Gemcitabine and cisplatin plus durvalumab with or without tremelimumab in chemotherapy-naïve patients with advanced biliary tract cancer: an open-label, single-centre, phase 2 study. *Lancet Gastroenterol Hepatol* 2022;7:522–532. doi: 10.1016/s2468-1253(22)00043-7.
123. Shi GM, Huang XY, Wu D, Sun HC, Liang F, Ji Y, *et al.* Toripalimab combined with lenvatinib and GEMOX is a promising regimen as first-line treatment for advanced intrahepatic cholangiocarcinoma: a single-center, single-arm, phase 2 study. *Signal Transduct Target Ther* 2023;8:106. doi: 10.1038/s41392-023-01317-7.
124. Wang L, Zhang N, Wang Y, Zhang T, Zhu W, Mao A, *et al.* Safety and efficacy of GEMOX plus donafenib and tislelizumab as first-line therapy for advanced epithelial malignant biliary tract cancer. *Cancer Med* 2023;12:12263–12271. doi: 10.1002/cam4.5924.
125. Shroff RT, Javle MM, Xiao L, Kaseb AO, Varadhachary GR, Wolff RA, *et al.* Gemcitabine, Cisplatin, and nab-Paclitaxel for the Treatment of Advanced Biliary Tract Cancers: A Phase 2 Clinical Trial. *JAMA Oncol* 2019;5:824–830. doi: 10.1001/jamaoncol.2019.0270.
126. Lee J, Park SH, Chang HM, Kim JS, Choi HJ, Lee MA, *et al.* Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2012;13:181–188. doi: 10.1016/s1470-2045(11)70301-1.
127. Leone F, Marino D, Cereda S, Filippi R, Belli C, Spadi R, *et al.* Panitumumab in combination with gemcitabine and oxaliplatin does not prolong survival in wild-type KRAS advanced biliary tract cancer: A randomized phase 2 trial (Vecti-BIL study). *Cancer* 2016;122:574–581. doi: 10.1002/cncr.29778.
128. Hezel AF, Noel MS, Allen JN, Abrams TA, Yurgelun M, Faris JE, *et al.* Phase II study of gemcitabine, oxaliplatin in combination with panitumumab in KRAS wild-type unresectable or metastatic biliary tract and gallbladder cancer. *Br J Cancer* 2014;111:430–436. doi: 10.1038/bjc.2014.343.
129. Nehls O, Oettle H, Hartmann JT, Hofheinz RD, Hass HG, Horger MS, *et al.* Capecitabine plus oxaliplatin as first-line treatment in patients with advanced biliary system adenocarcinoma: a prospective multicentre phase II trial. *Br J Cancer* 2008;98:309–315. doi: 10.1038/sj.bjc.6604178.
130. Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, *et al.* Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *Lancet Oncol* 2021;22:690–701. doi: 10.1016/s1470-2045(21)00027-9.
131. Yoo C, Kim KP, Jeong JH, Kim I, Kang MJ, Cheon J, *et al.* Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. *Lancet Oncol* 2021;22:1560–1572. doi: 10.1016/s1470-2045(21)00486-1.
132. Ramaswamy A, Ostwal V, Sharma A, Bhargava P, Srinivas S, Goel M, *et al.* Efficacy of Capecitabine Plus Irinotecan vs Irinotecan Monotherapy as Second-line Treatment in Patients With Advanced Gallbladder Cancer: A Multicenter Phase 2 Randomized Clinical Trial (GB-SELECT). *JAMA Oncol* 2021;7:436–439. doi: 10.1001/jamaoncol.2020.6166.
133. Javle MM, Oh DY, Ikeda M, Yong WP, Hsu K, Lindmark B, *et al.* Varlitinib plus capecitabine in second-line advanced biliary tract cancer: a randomized, phase II study (TreeTopp). *ESMO Open* 2022;7:100314. doi: 10.1016/j.esmoop.2021.100314.
134. Choi IS, Kim KH, Lee JH, Suh KJ, Kim JW, Park JH, *et al.* A randomised phase II study of oxaliplatin/5-FU (mFOLFOX) versus irinotecan/5-FU (mFOLFIRI) chemotherapy in locally advanced or metastatic biliary tract cancer refractory to first-line gemcitabine/cisplatin chemotherapy. *Eur J Cancer* 2021;154:288–295. doi: 10.1016/j.ejca.2021.06.019.
135. Demols A, Borbath I, Van den Eynde M, Houbiers G, Peeters M, Marechal R, *et al.* Regorafenib after failure of gemcitabine and platinum-based chemotherapy for locally advanced/metastatic biliary tumors: REACHIN, a randomized, double-blind, phase II trial. *Ann Oncol* 2020;31:1169–1177. doi: 10.1016/j.annonc.2020.05.018.
136. Zheng Y, Tu X, Zhao P, Jiang W, Liu L, Tong Z, *et al.* A randomised phase II study of second-line XELIRI regimen versus irinotecan monotherapy in advanced biliary tract cancer patients progressed on gemcitabine and cisplatin. *Br J Cancer* 2018;119:291–295. doi: 10.1038/s41416-018-0138-2.
137. Ueno M, Morizane C, Furukawa M, Sakai D, Komatsu Y, Nakai Y, *et al.* A randomized, double-blind, phase II study of oral histone deacetylase inhibitor resminostat plus S-1 versus placebo plus S-1 in biliary tract cancers previously treated with gemcitabine plus platinum-based chemotherapy. *Cancer Med* 2021;10:2088–2099. doi: 10.1002/cam4.3813.
138. Kim RD, McDonough S, El-Khoueiry AB, Bekaii-Saab TS, Stein SM, Sahai V, *et al.* Randomised phase II trial (SWOG S1310) of single agent MEK inhibitor trametinib Versus 5-fluorouracil or capecitabine in refractory advanced biliary cancer. *Eur J Cancer* 2020;130:219–227. doi: 10.1016/j.ejca.2020.01.026.
139. Xu J, Bai Y, Sun H, Bai C, Jia R, Li Y, *et al.* A single-arm, multicenter, open-label phase 2 trial of surufatinib in patients with unresectable or metastatic biliary tract cancer. *Cancer* 2021;127:3975–3984. doi: 10.1002/cncr.33803.
140. Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AE, *et al.* Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol* 2020;21:271–282. doi: 10.1016/s1470-2045(19)30691-6.
141. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, *et al.* Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. *N Engl J Med* 2018;378:731–739. doi: 10.1056/NEJMoa1714448.
142. Subbiah V, Wolf J, Konda B, Kang H, Spira A, Weiss J, *et al.* Tumour-agnostic efficacy and safety of selipratinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. *Lancet Oncol* 2022;23:1261–1273. doi: 10.1016/s1470-2045(22)00541-1.
143. Subbiah V, Cassier PA, Siena S, Garraza E, Paz-Ares L, Garrido P, *et al.* Pan-cancer efficacy of pralsetinib in patients with RET fusion-positive solid tumors from the phase 1/2 ARROW trial. *Nat Med* 2022;28:1640–1645. doi: 10.1038/s41591-022-01931-y.
144. Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, *et al.* Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol* 2020;21:671–684. doi: 10.1016/s1470-2045(20)30109-1.
145. Javle M, Roychowdhury S, Kelley RK, Sadeghi S, Macarulla T, Weiss KH, *et al.* Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study. *Lancet Gastroenterol Hepatol* 2021;6:803–815. doi: 10.1016/s2468-1253(21)00196-5.
146. El-Khoueiry AB, Ren Z, Chon H, Park JO, Kim JW, Pressiani T, *et al.* IMbrave151: A phase 2, randomized, double-blind, placebo-controlled study of atezolizumab with or without bevacizumab in combination with cisplatin plus gemcitabine in patients with untreated, advanced biliary tract cancer. *J Clin Oncol* 2023;41:491–491. doi: 10.1200/JCO.2023.41.4_suppl.491.
147. Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, *et al.* Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2020;21:796–807. doi: 10.1016/s1470-2045(20)30157-1.
148. Zhu AX, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, *et al.* Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With IDH1 Mutation: The Phase 3 Randomized Clinical ClarIDHy Trial. *JAMA Oncol* 2021;7:1669–1677. doi: 10.1001/jamaoncol.2021.3836.
149. Subbiah V, Lassen U, Élez E, Italiano A, Curigliano G, Javle M, *et al.* Dabrafenib plus trametinib in patients with BRAF(V600E)-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. *Lancet Oncol* 2020;21:1234–1243. doi: 10.1016/s1470-2045(20)30321-1.
150. Javle M, Borad MJ, Azad NS, Kurzrock R, Abou-Alfa GK, George B, *et al.* Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol* 2021;22:1290–1300. doi: 10.1016/s1470-2045(21)00336-3.
151. Harding JJ, Fan J, Oh DY, Choi HJ, Kim JW, Chang HM, *et al.* Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study. *Lancet Oncol* 2023;24:772–782. doi: 10.1016/s1470-2045(23)00242-5.

152. Lee CK, Chon HJ, Cheon J, Lee MA, Im HS, Jang JS, *et al.* Trastuzumab plus FOLFOX for HER2-positive biliary tract cancer refractory to gemcitabine and cisplatin: a multi-institutional phase 2 trial of the Korean Cancer Study Group (KCSG-HB19-14). *Lancet Gastroenterol Hepatol* 2023;8:56–65. doi: 10.1016/s2468-1253(22)00335-1.
153. Zhao Y, Yang M, Feng J, Wang X, Liu Y. Advances in immunotherapy for biliary tract cancers. *Chin Med J* 2024;137:524–532. doi: 10.1097/cm9.0000000000002759.
154. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, *et al.* Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017;357:409–413. doi: 10.1126/science.aan6733.
155. Chen X, Wu X, Wu H, Gu Y, Shao Y, Shao Q, *et al.* Camrelizumab plus gemcitabine and oxaliplatin (GEMOX) in patients with advanced biliary tract cancer: a single-arm, open-label, phase II trial. *J Immunother Cancer* 2020;8:e001240. doi: 10.1136/jitc-2020-001240.
156. Kim RD, Chung V, Alese OB, El-Rayes BF, Li D, Al-Toubah TE, *et al.* A Phase 2 Multi-institutional Study of Nivolumab for Patients With Advanced Refractory Biliary Tract Cancer. *JAMA Oncol* 2020;6:888–894. doi: 10.1001/jamaoncol.2020.0930.
157. Klein O, Kee D, Nagrial A, Markman B, Underhill C, Michael M, *et al.* Evaluation of Combination Nivolumab and Ipilimumab Immunotherapy in Patients With Advanced Biliary Tract Cancers: Subgroup Analysis of a Phase 2 Nonrandomized Clinical Trial. *JAMA Oncol* 2020;6:1405–1409. doi: 10.1001/jamaoncol.2020.2814.
158. Feng K, Liu Y, Guo Y, Qiu J, Wu Z, Dai H, *et al.* Phase I study of chimeric antigen receptor modified T cells in treating HER2-positive advanced biliary tract cancers and pancreatic cancers. *Protein Cell* 2018;9:838–847. doi: 10.1007/s13238-017-0440-4.
159. Parzen JS, Hartsell W, Chang J, Apisarnthanarax S, Molitoris J, Durci M, *et al.* Hypofractionated proton beam radiotherapy in patients with unresectable liver tumors: multi-institutional prospective results from the Proton Collaborative Group. *Radiat Oncol* 2020;15:255. doi: 10.1186/s13014-020-01703-3.
160. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol* 2012;30:1934–1940. doi: 10.1200/jco.2011.40.5381.
161. Chen Y, Zhang B, Liu C, Cao Y, Lyu C, Qiu M. Clinical efficacy of adjuvant treatments for patients with resected biliary tract cancer: a systematic review and network meta-analysis. *BMJ Open* 2022;12:e051421. doi: 10.1136/bmjopen-2021-051421.
162. Ren B, Guo Q, Yang Y, Liu L, Wei S, Chen W, *et al.* A meta-analysis of the efficacy of postoperative adjuvant radiotherapy versus no radiotherapy for extrahepatic cholangiocarcinoma and gallbladder carcinoma. *Radiat Oncol* 2020;15:15. doi: 10.1186/s13014-020-1459-x.
163. Kim BH, Kwon J, Chie EK, Kim K, Kim YH, Seo DW, *et al.* Adjuvant Chemoradiotherapy is Associated with Improved Survival for Patients with Resected Gallbladder Carcinoma: A Systematic Review and Meta-analysis. *Ann Surg Oncol* 2018;25:255–264. doi: 10.1245/s10434-017-6139-1.
164. Choi SH, Rim CH, Shin IS, Yoon WS, Koom WS, Seong J. Benefit of adjuvant radiotherapy for gallbladder cancer: a comparability-based meta-analysis. *Hepatol Int* 2022;16:712–727. doi: 10.1007/s12072-022-10343-6.
165. Bonet Beltrán M, Allal AS, Gich I, Solé JM, Carrió I. Is adjuvant radiotherapy needed after curative resection of extrahepatic biliary tract cancers? A systematic review with a meta-analysis of observational studies. *Cancer Treat Rev* 2012;38:111–119. doi: 10.1016/j.ctrv.2011.05.003.
166. Shi XQ, Zhang JY, Tian H, Tang LN, Li AL. Role of adjuvant (chemo)radiotherapy for resected extrahepatic cholangiocarcinoma: a meta-analysis. *J Zhejiang Univ Sci B* 2020;21:549–559. doi: 10.1631/jzus.B1900691.
167. Italian Clinical Practice Guidelines on Cholangiocarcinoma-Part II: Treatment. *Dig Liver Dis* 2020;52:1430–1442. doi: 10.1016/j.dld.2020.08.030.
168. Socha J, Michalak M, Wołakiewicz G, Kepka L. Nodal areas of potential geographic error in adjuvant radiotherapy for biliary tract cancer. *Radiother Oncol* 2017;125:365–373. doi: 10.1016/j.radonc.2017.09.025.
169. Marinelli I, Guido A, Fuccio L, Farioli A, Panni V, Giaccherini L, *et al.* Clinical Target Volume in Biliary Carcinoma: A Systematic Review of Pathological Studies. *Anticancer Res* 2017;37:955–961. doi: 10.21873/anticancer.11404.
170. Kobayashi S, Tomokuni A, Gotoh K, Takahashi H, Akita H, Marubashi S, *et al.* A retrospective analysis of the clinical effects of neoadjuvant combination therapy with full-dose gemcitabine and radiation therapy in patients with biliary tract cancer. *Eur J Surg Oncol* 2017;43:763–771. doi: 10.1016/j.ejso.2016.12.008.
171. Jung JH, Lee HJ, Lee HS, Jo JH, Cho IR, Chung MJ, *et al.* Benefit of neoadjuvant concurrent chemoradiotherapy for locally advanced perihilar cholangiocarcinoma. *World J Gastroenterol* 2017;23:3301–3308. doi: 10.3748/wjg.v23.i18.3301.
172. Grendar J, Grendarova P, Sinha R, Dixon E. Neoadjuvant therapy for downstaging of locally advanced hilar cholangiocarcinoma: a systematic review. *HPB (Oxford)* 2014;16:297–303. doi: 10.1111/hpb.12150.
173. Sahai P, Kumar S. External radiotherapy and brachytherapy in the management of extrahepatic and intrahepatic cholangiocarcinoma: available evidence. *Br J Radiol* 2017;90:20170061. doi: 10.1259/bjr.20170061.
174. Shao F, Qi W, Meng FT, Qiu L, Huang Q. Role of palliative radiotherapy in unresectable intrahepatic cholangiocarcinoma: population-based analysis with propensity score matching. *Cancer Manag Res* 2018;10:1497–1506. doi: 10.2147/cmar.S160680.
175. Jackson MW, Amini A, Jones BL, Rusthoven CG, Scheffer TE, Goodman KA. Treatment Selection and Survival Outcomes With and Without Radiation for Unresectable, Localized Intrahepatic Cholangiocarcinoma. *Cancer J* 2016;22:237–242. doi: 10.1097/ppo.0000000000000213.
176. Torgeson A, Lloyd S, Boothe D, Cannon G, Garrido-Laguna I, Whisenant J, *et al.* Chemoradiation Therapy for Unresected Extrahepatic Cholangiocarcinoma: A Propensity Score-Matched Analysis. *Ann Surg Oncol* 2017;24:4001–4008. doi: 10.1245/s10434-017-6131-9.
177. Chang WW, Hsiao PK, Qin L, Chang CL, Chow JM, Wu SY. Treatment outcomes for unresectable intrahepatic cholangiocarcinoma: Nationwide, population-based, cohort study based on propensity score matching with the Mahalanobis metric. *Radiother Oncol* 2018;129:284–292. doi: 10.1016/j.radonc.2018.09.010.
178. Alam MN, Agrawal S, Rastogi N, Maria Das KJ. Consolidation chemoradiation (cCIRT) improves survival in responders to first-line chemotherapy (CT) in locally advanced gallbladder cancer (LA-GBC): A new standard of care? *Indian J Cancer* 2022;59:577–583. doi: 10.4103/ijc.IJC_1145_20.
179. Sinha S, Engineer R, Ostwal V, Ramaswamy A, Chopra S, Shetty N. Radiotherapy for locally advanced unresectable gallbladder cancer - A way forward: Comparative study of chemotherapy versus chemoradiotherapy. *J Cancer Res Ther* 2022;18:147–151. doi: 10.4103/jcrt.JCRT_1568_20.
180. Kim YI, Park JW, Kim BH, Woo SM, Kim TH, Koh YH, *et al.* Outcomes of concurrent chemoradiotherapy versus chemotherapy alone for advanced-stage unresectable intrahepatic cholangiocarcinoma. *Radiat Oncol* 2013;8:292. doi: 10.1186/1748-717x-8-292.
181. Chen YX, Zeng ZC, Tang ZY, Fan J, Zhou J, Jiang W, *et al.* Determining the role of external beam radiotherapy in unresectable intrahepatic cholangiocarcinoma: a retrospective analysis of 84 patients. *BMC Cancer* 2010;10:492. doi: 10.1186/1471-2407-10-492.
182. Zeng ZC, Tang ZY, Fan J, Zhou J, Qin LX, Ye SL, *et al.* Consideration of the role of radiotherapy for unresectable intrahepatic cholangiocarcinoma: a retrospective analysis of 75 patients. *Cancer J* 2006;12:113–122.
183. Lee J, Yoon WS, Koom WS, Rim CH. Efficacy of stereotactic body radiotherapy for unresectable or recurrent cholangiocarcinoma: a meta-analysis and systematic review. *Strahlenther Onkol* 2019;195:93–102. doi: 10.1007/s00066-018-1367-2.
184. Brunner TB, Blanck O, Lewitzki V, Abbasi-Senger N, Momm F, Riesterer O, *et al.* Stereotactic body radiotherapy dose and its impact on local control and overall survival of patients for locally advanced intrahepatic and extrahepatic cholangiocarcinoma. *Radiother Oncol* 2019;132:42–47. doi: 10.1016/j.radonc.2018.11.015.
185. Tao R, Krishnan S, Bhosale PR, Javle MM, Aloia TA, Shroff RT, *et al.* Ablative Radiotherapy Doses Lead to a Substantial Prolongation of Survival in Patients With Inoperable Intrahepatic Cholangiocarcinoma: A Retrospective Dose Response Analysis. *J Clin Oncol* 2016;34:219–226. doi: 10.1200/jco.2015.61.3778.
186. Autorino R, Mattiucci GC, Ardito F, Balducci M, Deodato F, Macchia G, *et al.* Radiochemotherapy with Gemcitabine in Unre-

- sectable Extrahepatic Cholangiocarcinoma: Long-term Results of a Phase II Study. *Anticancer Res* 2016;36:737–740.
187. Phelip JM, Vendrely V, Rostain F, Subtil F, Jouve JL, Gasmi M, *et al.* Gemcitabine plus cisplatin versus chemoradiotherapy in locally advanced biliary tract cancer: Fédération Francophone de Cancérologie Digestive 9902 phase II randomised study. *European Journal of Cancer* 2014; 50: 2975–2982.
 188. Dumonceau JM, Tringali A, Papanikolaou IS, Blero D, Mangiavillano B, Schmidt A, *et al.* Endoscopic biliary stenting: indications, choice of stents, and results: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline - Updated October 2017. *Endoscopy* 2018;50:910–930. doi: 10.1055/a-0659-9864.
 189. Matsunaga Y, Higuchi R, Yazawa T, Uemura S, Izumo W, Ota T, *et al.* Negative prognostic outcomes of percutaneous transhepatic biliary drainage in distal cholangiocarcinoma: a retrospective analysis using propensity score matching. *Int J Clin Oncol* 2021;26:1492–1499. doi: 10.1007/s10147-021-01926-8.
 190. Mori S, Aoki T, Park KH, Shiraki T, Sakuraoka Y, Iso Y, *et al.* Impact of preoperative percutaneous transhepatic biliary drainage on post-operative survival in patients with distal cholangiocarcinoma. *ANZ J Surg* 2019;89:E363–e367. doi: 10.1111/ans.15329.
 191. Miura F, Sano K, Wada K, Shibuya M, Ikeda Y, Takahashi K, *et al.* Prognostic impact of type of preoperative biliary drainage in patients with distal cholangiocarcinoma. *Am J Surg* 2017;214:256–261. doi: 10.1016/j.amjsurg.2017.01.010.
 192. Komaya K, Ebata T, Fukami Y, Sakamoto E, Miyake H, Takara D, *et al.* Percutaneous biliary drainage is oncologically inferior to endoscopic drainage: a propensity score matching analysis in resectable distal cholangiocarcinoma. *J Gastroenterol* 2016;51:608–619. doi: 10.1007/s00535-015-1140-6.
 193. Inamdar S, Slattery E, Bhalla R, Seipal DV, Trindade AJ. Comparison of Adverse Events for Endoscopic vs Percutaneous Biliary Drainage in the Treatment of Malignant Biliary Tract Obstruction in an Inpatient National Cohort. *JAMA Oncol* 2016;2:112–117. doi: 10.1001/jamaoncol.2015.3670.
 194. Rerknimitr R, Angsuwatcharakon P, Ratanachu-ek T, Khor CJ, Ponnudurai R, Moon JH, *et al.* Asia-Pacific consensus recommendations for endoscopic and interventional management of hilar cholangiocarcinoma. *J Gastroenterol Hepatol* 2013;28:593–607. doi: 10.1111/jgh.12128.
 195. Elmunzer BJ, Smith ZL, Tarnasky P, Wang AY, Yachimski P, Banovac F, *et al.* An Unsuccessful Randomized Trial of Percutaneous vs Endoscopic Drainage of Suspected Malignant Hilar Obstruction. *Clin Gastroenterol Hepatol* 2021;19:1282–1284. doi: 10.1016/j.cgh.2020.05.035.
 196. Coelen RJS, Roos E, Wiggers JK, Besselink MG, Buis CI, Busch ORC, *et al.* Endoscopic versus percutaneous biliary drainage in patients with resectable perihilar cholangiocarcinoma: a multicentre, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2018;3:681–690. doi: 10.1016/s2468-1253(18)30234-6.
 197. Moll CF, de Moura DTH, Ribeiro IB, Proença IM, do Monte Junior ES, Sánchez-Luna SA, *et al.* Endoscopic Biliary Drainage (EBD) versus Percutaneous Transhepatic Biliary Drainage (PTBD) for biliary drainage in patients with Perihilar Cholangiocarcinoma (PCCA): A systematic review and meta-analysis. *Clinics (Sao Paulo)* 2023;78:100163. doi: 10.1016/j.clinsp.2022.100163.
 198. Hajibandeh S, Hajibandeh S, Satyadas T. Endoscopic Versus Percutaneous Preoperative Biliary Drainage in Patients With Klatskin Tumor Undergoing Curative Surgery: A Systematic Review and Meta-Analysis of Short-Term and Long-Term Outcomes. *Surg Innov* 2020;27:279–290. doi: 10.1177/1553350620911291.
 199. Wang L, Lin N, Xin F, Ke Q, Zeng Y, Liu J. A systematic review of the comparison of the incidence of seeding metastasis between endoscopic biliary drainage and percutaneous transhepatic biliary drainage for resectable malignant biliary obstruction. *World J Surg Oncol* 2019;17:116. doi: 10.1186/s12957-019-1656-y.
 200. Gao DJ, Yang JF, Ma SR, Wu J, Wang TT, Jin HB, *et al.* Endoscopic radiofrequency ablation plus plastic stent placement versus stent placement alone for unresectable extrahepatic biliary cancer: a multicenter randomized controlled trial. *Gastrointest Endosc* 2021;94:91–100.e102. doi: 10.1016/j.gie.2020.12.016.
 201. Yang J, Wang J, Zhou H, Zhou Y, Wang Y, Jin H, *et al.* Efficacy and safety of endoscopic radiofrequency ablation for unresectable extrahepatic cholangiocarcinoma: a randomized trial. *Endoscopy* 2018;50:751–760. doi: 10.1055/s-0043-124870.
 202. Cha BH, Jang MJ, Lee SH. Survival Benefit of Intraductal Radiofrequency Ablation for Malignant Biliary Obstruction: A Systematic Review with Meta-Analysis. *Clin Endosc* 2021;54:100–106. doi: 10.5946/ce.2020.254.
 203. de Jong DM, Fritzsche JA, Audhoe AS, Yi SSL, Bruno MJ, Voermans RP, *et al.* Comparison of Intraductal RFA Plus Stent versus Stent-Only Treatment for Unresectable Perihilar Cholangiocarcinoma-A Systematic Review and Meta-Analysis. *Cancers (Basel)* 2022;14:2079. doi: 10.3390/cancers14092079.
 204. Mohan BP, Chandan S, Khan SR, Kassab LL, Ponnada S, Artifon ELA, *et al.* Photodynamic Therapy (PDT), Radiofrequency Ablation (RFA) With Biliary Stents in Palliative Treatment of Unresectable Extrahepatic Cholangiocarcinoma: A Systematic Review and Meta-analysis. *J Clin Gastroenterol* 2022;56:e153–e160. doi: 10.1097/mcg.0000000000001524.
 205. Rebhun J, Shin CM, Siddiqui UD, Villa E. Endoscopic biliary treatment of unresectable cholangiocarcinoma: A meta-analysis of survival outcomes and systematic review. *World J Gastrointest Endosc* 2023;15:177–190. doi: 10.4253/wjge.v15.i3.177.
 206. Sofi AA, Khan MA, Das A, Sachdev M, Khuder S, Nawras A, *et al.* Radiofrequency ablation combined with biliary stent placement versus stent placement alone for malignant biliary strictures: a systematic review and meta-analysis. *Gastrointest Endosc* 2018;87:944–951.e941. doi: 10.1016/j.gie.2017.10.029.
 207. Song S, Jin H, Cheng Q, Gong S, Lv K, Lei T, *et al.* Local palliative therapies for unresectable malignant biliary obstruction: radiofrequency ablation combined with stent or biliary stent alone? An updated meta-analysis of nineteen trials. *Surg Endosc* 2022;36:5559–5570. doi: 10.1007/s00464-022-09181-2.
 208. Zheng X, Bo ZY, Wan W, Wu YC, Wang TT, Wu J, *et al.* Endoscopic radiofrequency ablation may be preferable in the management of malignant biliary obstruction: A systematic review and meta-analysis. *J Dig Dis* 2016;17:716–724. doi: 10.1111/1751-2980.12429.
 209. Chen P, Yang T, Shi P, Shen J, Feng Q, Su J. Benefits and safety of photodynamic therapy in patients with hilar cholangiocarcinoma: A meta-analysis. *Photodiagnosis Photodyn Ther* 2022;37:102712. doi: 10.1016/j.pdpdt.2022.102712.
 210. Gao F, Bai Y, Ma SR, Liu F, Li ZS. Systematic review: photodynamic therapy for unresectable cholangiocarcinoma. *J Hepatobiliary Pancreat Sci* 2010;17:125–131. doi: 10.1007/s00534-009-0109-3.
 211. Moole H, Tathireddy H, Dharmapuri S, Moole V, Boddireddy R, Yedama P, *et al.* Success of photodynamic therapy in palliating patients with nonresectable cholangiocarcinoma: A systematic review and meta-analysis. *World J Gastroenterol* 2017;23:1278–1288. doi: 10.3748/wjg.v23.i7.1278.
 212. Albers D, Schmidt A, Schiemer M, Caca K, Wannhoff A, Sauer P, *et al.* Impact of endobiliary radiofrequency ablation on biliary drainage in patients with malignant biliary strictures treated with uncovered self-expandable metal stents: a randomized controlled multicenter trial. *Gastrointest Endosc* 2022;96:970–979. doi: 10.1016/j.gie.2022.05.022.
 213. Kang H, Han SY, Cho JH, Kim EJ, Kim DU, Yang JK, *et al.* Efficacy and safety of temperature-controlled intraductal radiofrequency ablation in advanced malignant hilar biliary obstruction: A pilot multicenter randomized comparative trial. *J Hepatobiliary Pancreat Sci* 2022;29:469–478. doi: 10.1002/jhbp.1082.
 214. Beyer F, Rice S, Orozco-Leal G, Still M, O’Keefe H, O’Connor N, *et al.* Clinical and cost effectiveness of endoscopic bipolar radiofrequency ablation for the treatment of malignant biliary obstruction: a systematic review. *Health Technol Assess* 2023;27:1–118. doi: 10.3310/yymn9802.
 215. Ortner ME, Caca K, Berr F, Liebetruht J, Mansmann U, Huster D, *et al.* Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. *Gastroenterology* 2003;125:1355–1363. doi: 10.1016/j.gastro.2003.07.015.
 216. Zoepf T, Jakobs R, Arnold JC, Apel D, Riemann JF. Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy. *Am J Gastroenterol* 2005;100:2426–2430. doi: 10.1111/j.1572-0241.2005.00318.x.
 217. Dumoulin FL, Gerhardt T, Fuchs S, Scheurlen C, Neubrand M, Layer G, *et al.* Phase II study of photodynamic therapy and metal stent as palliative treatment for nonresectable hilar cholangiocarcinoma. *Gastrointest Endosc* 2003;57:860–867. doi: 10.1016/s0016-5107(03)70021-2.
 218. Kahaleh M, Mishra R, Shami VM, Northup PG, Berg CL, Bashlor P, *et al.* Unresectable cholangiocarcinoma: comparison of survival in biliary stenting alone versus stenting with photodynamic therapy. *Clin Gastroenterol Hepatol* 2008;6:290–297. doi: 10.1016/j.cgh.2007.12.004.

219. Li Z, Jiang X, Xiao H, Chen S, Zhu W, Lu H, *et al.* Long-term results of ERCP- or PTCS-directed photodynamic therapy for unresectable hilar cholangiocarcinoma. *Surg Endosc* 2021;35:5655–5664. doi: 10.1007/s00464-020-08095-1.
220. Witzigmann H, Berr F, Ringel U, Caca K, Uhlmann D, Schoppmeyer K, *et al.* Surgical and palliative management and outcome in 184 patients with hilar cholangiocarcinoma: palliative photodynamic therapy plus stenting is comparable to r1/r2 resection. *Ann Surg* 2006;244:230–239. doi: 10.1097/01.sla.0000217639.10331.47.
221. Yang J, Shen H, Jin H, Lou Q, Zhang X. Treatment of unresectable extrahepatic cholangiocarcinoma using hematoporphyrin photodynamic therapy: A prospective study. *Photodiagnosis Photodyn Ther* 2016;16:110–118. doi: 10.1016/j.pdpdt.2016.10.001.
222. Yu Y, Wang N, Wang Y, Shi Q, Yu R, Gu B, *et al.* Photodynamic therapy combined with systemic chemotherapy for unresectable extrahepatic cholangiocarcinoma: A systematic review and meta-analysis. *Photodiagnosis Photodyn Ther* 2023;41:103318. doi: 10.1016/j.pdpdt.2023.103318.
223. Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, *et al.* The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. *Pain* 2019;160:53–59. doi: 10.1097/j.pain.0000000000001365.
224. McGuire LS, Slavin K. Revisiting the WHO Analgesic Ladder for Surgical Management of Pain. *AMA J Ethics* 2020;22:E695–701. doi: 10.1001/amajethics.2020.695.
225. Brogan S, Junkins S. Interventional therapies for the management of cancer pain. *J Support Oncol* 2010;8:52–59.
226. Tay W, Ho KY. The role of interventional therapies in cancer pain management. *Ann Acad Med Singap* 2009;38:989–997.
227. Goetz MP, Callstrom MR, Charboneau JW, Farrell MA, Maus TP, Welch TJ, *et al.* Percutaneous image-guided radiofrequency ablation of painful metastases involving bone: a multicenter study. *J Clin Oncol* 2004;22:300–306. doi: 10.1200/jco.2004.03.097.
228. Kashima M, Yamakado K, Takaki H, Kaminou T, Tanigawa N, Nakatsuka A, *et al.* Radiofrequency ablation for the treatment of bone metastases from hepatocellular carcinoma. *AJR Am J Roentgenol* 2010;194:536–541. doi: 10.2214/ajr.09.2975.
229. Kim SH, Lee SM, Jeung HC, Lee IJ, Park JS, Song M, *et al.* The Effect of Nutrition Intervention with Oral Nutritional Supplements on Pancreatic and Bile Duct Cancer Patients Undergoing Chemotherapy. *Nutrients* 2019;11:1145. doi: 10.3390/nu11051145.
230. Born P, Rösch T, Brühl K, Sandsch W, Weigert N, Ott R, *et al.* Long-term outcome in patients with advanced hilar bile duct tumors undergoing palliative endoscopic or percutaneous drainage. *Z Gastroenterol* 2000;38:483–489. doi: 10.1055/s-2000-14886.

How to cite this article: Wang XA, Bai YR, Chai NL, Li YX, Linghu EQ, Wang LW, Liu YB; Society of Hepato-pancreato-biliary Surgery of Chinese Research Hospital Association, Society of Digestive Endoscopy of the Chinese Medical Association, *Chinese Medical Journal Clinical Practice Guideline Collaborative*. Chinese national clinical practice guideline on diagnosis and treatment of biliary tract cancers. *Chin Med J* 2024;137:2272–2293. doi: 10.1097/CM9.0000000000003258