BMJ Best Practice

Cholangiocarcinoma

Straight to the point of care

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Summary

Cholangiocarcinoma may be asymptomatic in the early stages. Classic symptoms of painless jaundice, weight loss, and abdominal pain usually appear in advanced disease.

Liver enzymes, blood levels of carbohydrate antigen (CA) 19-9, carcinoembryonic antigen, CA-125; abdominal ultrasound, abdominal CT/MRI, and endoscopic ultrasound are used for evaluation.

Surgical resection offers the only potential cure for early-stage disease.

Chemotherapy with or without immunotherapy may have a positive effect on overall survival of patients following resection of cholangiocarcinoma.

Liver transplant is indicated in a small subset of patients.

Definition

Cholangiocarcinomas are cancers arising from the bile duct epithelium. These can be divided depending on their location in the biliary tree: intrahepatic or extrahepatic (perihilar and distal). Perihilar tumors involving the bifurcation of the ducts are also known as Klatskin tumors. More than 95% are adenocarcinomas. Most are of the infiltrating nodular or diffusely infiltrating type. Purely nodular or papillary are less frequent subtypes.

Epidemiology

Approximately two-thirds of cholangiocarcinomas occur in patients ages between 50 and 70 years, with a slight male predominance.[4] The reported incidence of biliary tumors has increased in recent years; however, the increase is probably due to improvement in data collection and analysis.

The incidence varies worldwide. The highest known rates occur in north-east Thailand (>80 per 100,000 population).[2] High rates of biliary cancer are also seen in South American countries (Bolivia, Chile) and northern Japan. Intermediate rates are seen in many European countries, and low rates are observed in the US, the UK, India, Nigeria, and Singapore.[5] The lowest rates are seen in Canada (0.3 per 100,000).[2] In the US, New Mexico has the highest incidence of biliary tree carcinoma (gallbladder carcinoma accounts for 8.5% of all cancers).[6]

Etiology

There is a close association between infection, inflammation, and cancer. Multiple risk factors, particularly those linked to chronic biliary inflammation, are associated with cholangiocarcinoma.[7] [8] Some risk factors are relevant to all types of cholangiocarcinoma, while others are specific to different subtypes of the disease. For example, conditions that are associated with an increased risk of developing intrahepatic cholangiocarcinoma include chronic liver disease due to hepatitis B or C leading to cirrhosis, alcoholic liver disease, nonspecific cirrhosis, bile duct diseases (e.g., bile duct adenoma, biliary papillomatosis, and congenital liver abnormalities such as choledochal cyst and Caroli disease), choledocholithiasis, cholecystolithiasis, ulcerative colitis, and HIV.[7] [9] [10] [11] [12] [13]

Primary sclerosing cholangitis (PSC) has also been associated with high risk of cholangiocarcinoma, with a prevalence in patients with PSC ranging from 7% to 13%.[14] The risk of cholangiocarcinoma in patients with PSC increases with older age.[7]

Risk factors for both intra- and extrahepatic cholangiocarcinoma include chronic typhoid carriers, infection with liver flukes (*Clonorchis sinensis* and *Opisthorchis*), heavy drinking (>80 g of ethanol per day), exposure to certain toxins/medications (e.g., polychlorinated biphenyls [PCBs], isoniazid, and oral contraceptive pills), and the use of radionuclides (thorium dioxide, a radioactive contrast agent used until the 1950s).[15] [16] [17][18]

Pathophysiology

Cholangiocarcinomas are uncommon and, depending on the site of the cancer, the etiologic risk factors, patient characteristics, and molecular biology of the tumor vary. Despite the remarkable advances that have occurred in the understanding of cancer biology and genetics, little is known about the molecular biology of biliary tract cancers. Reports have associated genetic mutations with the cellular mechanisms that have an important role in the development of these tumors. Point mutations of K-ras and beta-catenin proto-oncogenes, and alterations of p53, p16, APC, and DPC4 tumor suppressor genes by a combination of chromosomal deletion, mutation, or methylation have been associated with biliary tract tumors.[19]

More than 95% of biliary tract cancers are adenocarcinomas. Most are of the infiltrating nodular or diffusely infiltrating type. Purely nodular or papillary are less frequent subtypes. These tumors produce a desmoplastic reaction resulting in a low neoplastic cellularity. This makes establishing a diagnosis difficult with small

biopsies. Staining for carcinoembryonic antigen (CEA), CA 19-9, or CA-50 aids in making a pathologic diagnosis.[6] [9] [14] [20]

Signaling pathways, drivers of carcinogenesis, and potential targets for therapies include KRAS/MAPK, EGFR, IL-6/STAT, IDH1/2, FGFR2, and MET signaling.[2] No oncogenic addiction loops have been described so far. Molecular classification of iCCA based on gene signatures or molecular abnormalities is not ready for clinical application.

Classification

American Joint Committee on Cancer TNM staging system (8th Edition)[1]

The American Joint Committee on Cancer (AJCC) staging system describes the extent of disease based on the following anatomic factors: size and extent of the primary tumor (T); regional lymph node involvement (N); and presence or absence of distant metastases (M). Nonanatomic prognostic factors (e.g., tumor grade, biomarkers) may be used to supplement the staging of certain cancers.

International Liver Cancer Association[2]

Guidelines from the International Liver Cancer Association recommend that cholangiocarcinoma should be subclassified as intrahepatic (iCCA), perihilar (pCCA), or distal (dCCA), where iCCA arises within the liver parenchyma. The terms "Klatskin tumor" and "extrahepatic tumor" are discouraged.

Bismuth-Corlette: hilar cholangiocarcinoma[3]

The extent of duct involvement by perihilar tumors can be classified as suggested by Bismuth:

- Type 1 - tumors below the confluence of the left and right duct
- Type 2 - tumors reaching the confluence but not involving the left or right hepatic ducts
- Type 3 - tumors occluding the common hepatic duct and either the right (3a) or left (3b) hepatic duct
- Type 4 - tumors that are multicentric or that involve the confluence and both the right and left hepatic ducts.

Case history

Case history #1

A 65-year-old woman presents to her primary care physician with a 4-month history of intermittent abdominal pain localized to the right upper quadrant (RUQ) with radiation to the epigastrium; the pain increases with the ingestion of fatty food and decreases with fasting. In the last 2 weeks the pain has been more frequent and steady. The patient complains of nausea, pruritus, anorexia, and weight loss, which she relates to the lack of appetite. At physical examination, there is RUQ tenderness and jaundice of the conjunctival sclera. No lymphadenopathy or palpable masses are found.

Other presentations

The clinical diagnosis of biliary tract tumors is very difficult due to lack of specific symptoms. When the classic symptoms (jaundice, weight loss, anorexia, and right upper quadrant pain) appear, the disease is usually in a more advanced stage. The clinical presentation depends largely on the location of the tumor, and the presence or absence of obstructive jaundice. Patients with early tumors that have not yet obstructed the bile duct may present with vague abdominal pain and LFT abnormalities. In advanced cases of distal extrahepatic cholangiocarcinoma, a distended palpable gallbladder may be present without pain and obstructive jaundice (Courvoisier sign).

Approach

Cholangiocarcinoma usually presents late, with advanced disease. The clinical presentation depends largely on the location of the tumor: that is, intrahepatic or extrahepatic (perihilar and distal). Some cholangiocarcinomas are found unexpectedly as a result of an ultrasound scan or liver profile performed for a different reason. However, imaging alone is not sufficient to make a diagnosis. Pathologic diagnosis of operative specimens is required for a definitive diagnosis.[7]

History and physical examination

The typical patient is usually ages >50 years. Other key risk factors that should be elicited during history-taking include history of cholangitis, choledocholithiasis, cholecystolithiasis, other structural disorders of the biliary tract, ulcerative colitis, primary sclerosing cholangitis, liver fluke infection, liver disease, hepatitis C virus, HIV infection, hepatitis B virus, and exposure to thorium dioxide or other toxins/medications (e.g., polychlorinated biphenyls [PCBs], isoniazid, oral contraceptive pills, and to chronic typhoid carriers).

Intrahepatic cholangiocarcinoma

- Usually presents as a mass lesion; obstructive jaundice symptoms are rare. Some nonspecific symptoms, such as abdominal discomfort, malaise, and nausea, can be present.

Extrahepatic cholangiocarcinoma (perihilar and distal)

- Usually presents with the symptoms of obstructive jaundice (around 90% of patients): pale stool, dark urine, and pruritus. During the early stages of the tumor, when the biliary tract has not been obstructed, some nonspecific symptoms including vague abdominal pain, nausea, and malaise can be present. In advanced disease, jaundice, pruritus, weight loss, anorexia, fatigue, abdominal mass, hepatomegaly, and Courvoisier sign (painless palpable gallbladder and jaundice) may be present.[3] [30] [31]

Laboratory investigations

No blood tests are diagnostic for cholangiocarcinoma. Liver function tests (LFTs) should be ordered, as liver biochemical abnormalities are consistent with obstructive jaundice. Certain serum tumor markers have shown some utility as an aid to other diagnostic tests; however, they are not used as a screening test because of the lack of sensitivity and specificity.

It is recommended that the following blood tests are ordered:

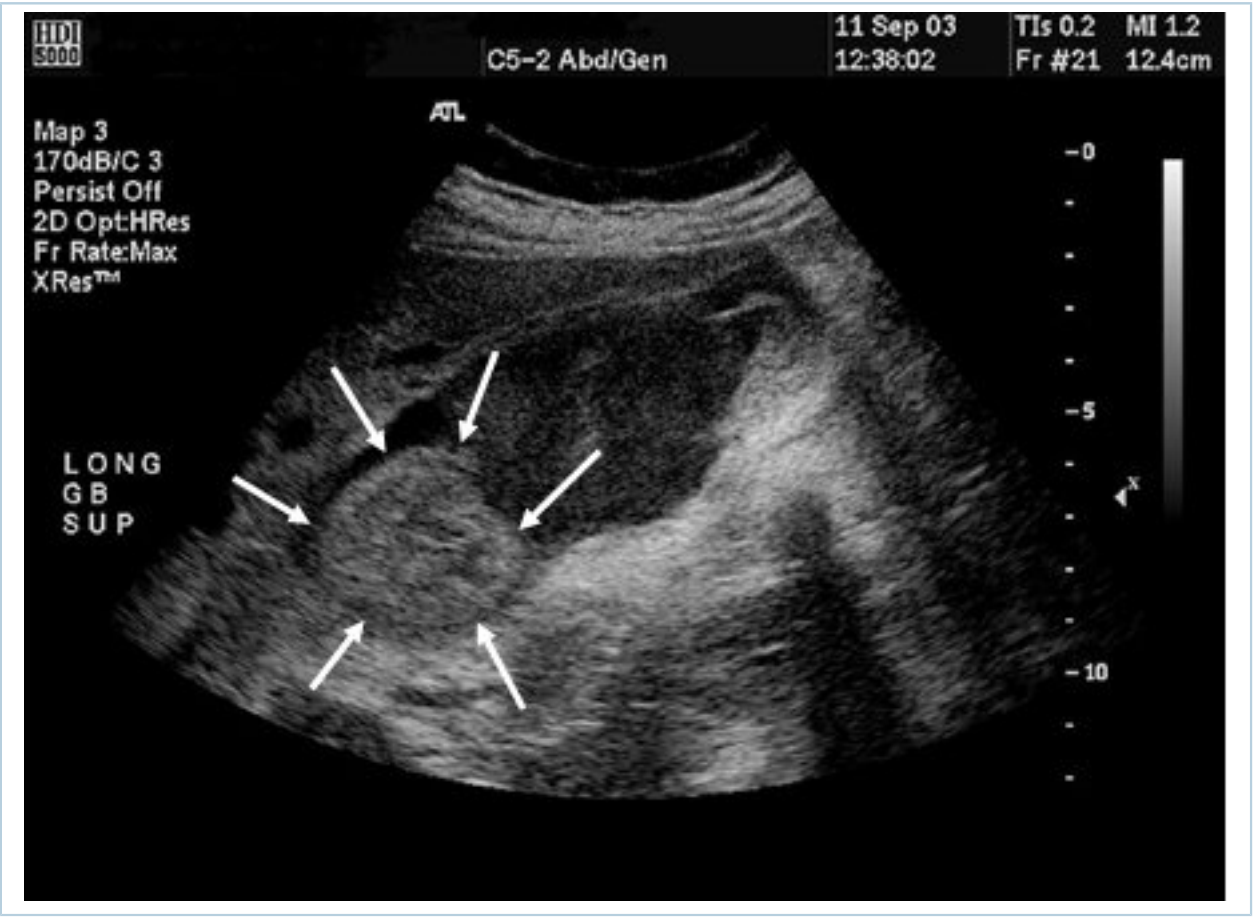
- Bilirubin (conjugated bilirubin is elevated in obstructive jaundice)
- Alk phos (usually elevated; suggests obstructive [or cholestatic] pattern of elevated LFTs)
- Gamma-GT (usually elevated; suggests obstructive [or cholestatic] pattern of elevated LFTs)
- Aminotransferase (may be minimally elevated)
- Prothrombin time (usually increased)
- CA 19-9 (elevated in up to 85% of patients)
- CA-125 (elevated; detectable in up to 65% of patients)
- CEA (elevated)

Imaging

A specific challenge in the management of cholangiocarcinoma is the lack of reliable imaging. No consensus exists about the various combinations of imaging modalities. Typically, ultrasound is followed by computed tomography (CT) or magnetic resonance imaging (MRI). High-resolution cross-sectional imaging of the liver is essential for evaluation of the primary mass, presence of metastases, vascular invasion, resectability, and accurate staging.[7] [32]

Abdominal ultrasound

The initial test to evaluate a patient with obstructive jaundice. This is because of the ubiquitous availability of this modality and the capacity to exclude common causes, such as choledocholithiasis. Ultrasound allows for the visualization of the intrahepatic and extrahepatic biliary ducts, thus demonstrating the level of potential obstruction as well as the caliber and patency of the portal vasculature. However, the sensitivity of ultrasound in specifically detecting cholangiocarcinoma is low.[32] When additional criteria are employed, such as clinical history and presenting symptoms, a focused ultrasound to evaluate the biliary tree and portal venous structures can have a high sensitivity. However, used alone, ultrasound has a low level of accuracy in assessing any specific diagnoses.



Gallbladder ultrasound of mass (arrows)

From the collection of Dr Joseph Espat; used with permission

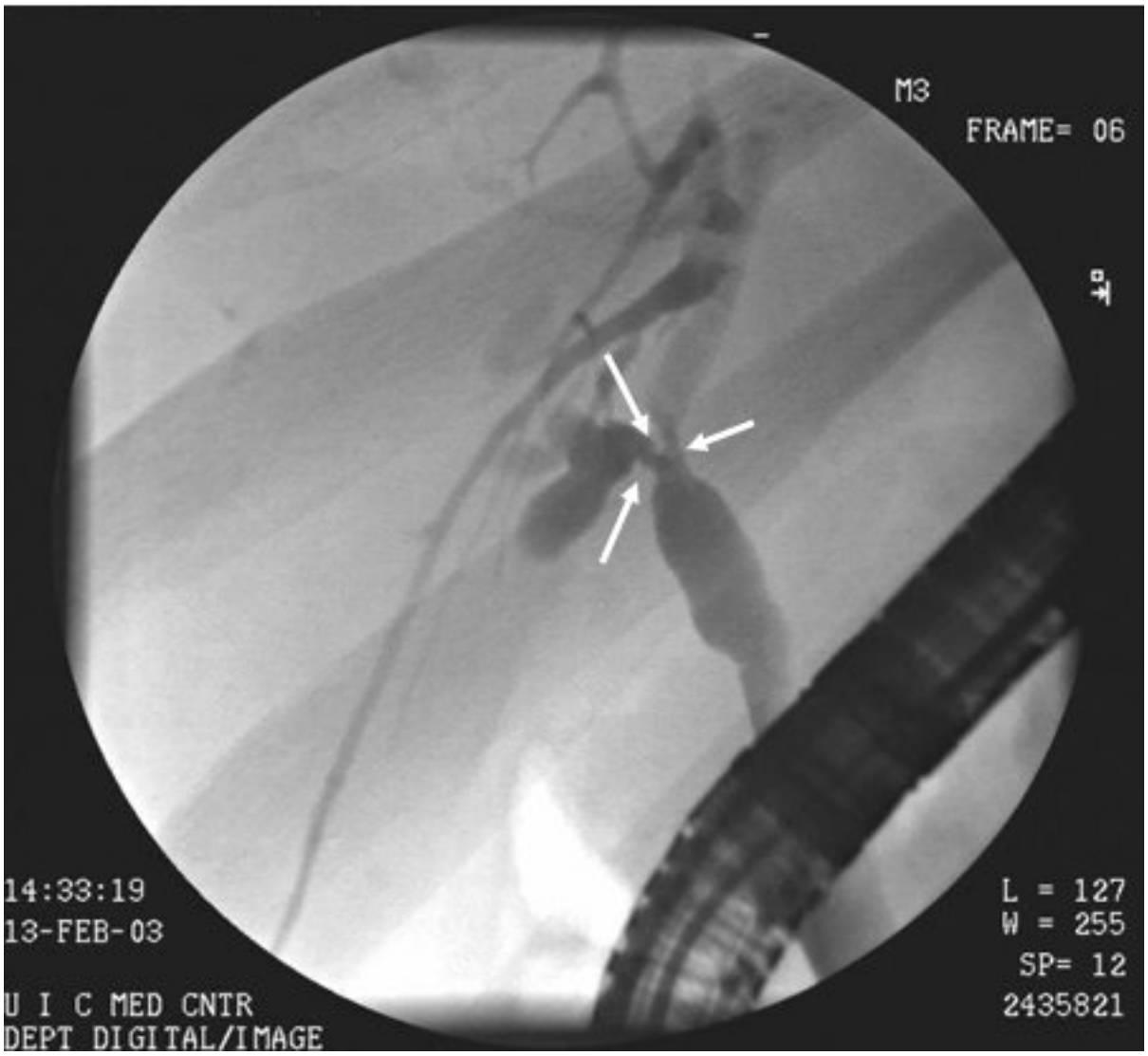
Abdominal CT/MRI

Ultrasound is usually followed by an abdominal CT, which will confirm the presence of a mass and whether or not there is obstruction, manifested as intrahepatic or extrahepatic ductal dilation. Abdominal

MRI is often utilized to differentiate between solid and cystic biliary contents. Furthermore, MRI can provide additional information regarding tumor size, extent of bile duct involvement, vascular patency, extrahepatic extension, nodal or distant metastases, and the presence of lobar atrophy. MRI diagnostic performance is comparable to CT.[33] Preoperative imaging with MR angiography is a noninvasive method for staging cholangiocarcinoma, and therefore also helps determine resectability.[34]

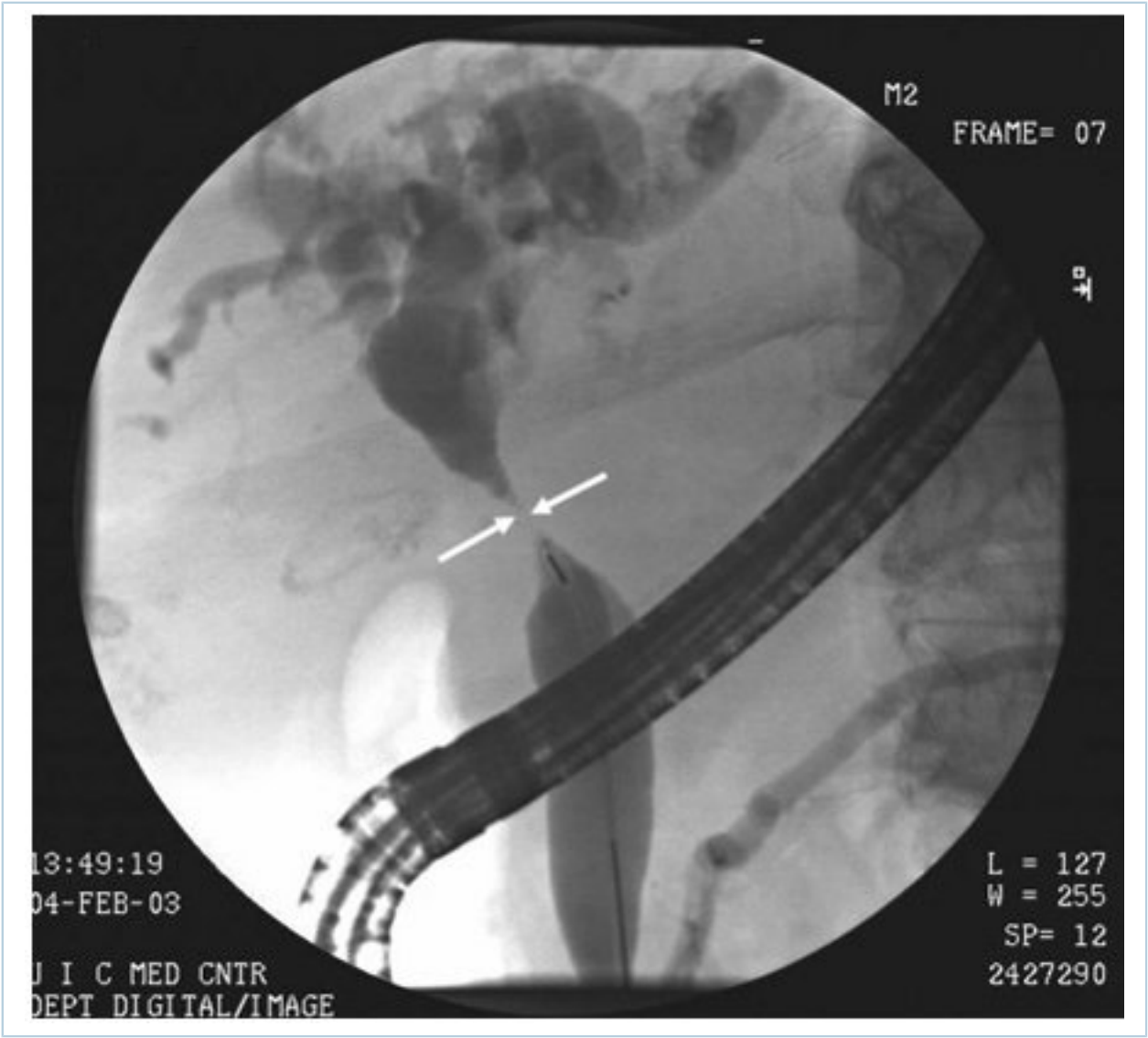
Cholangiography

Imaging findings are then correlated with laboratory findings, and if a provisional diagnosis of cholangiocarcinoma is made, the patient may have further imaging by endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), or percutaneous transhepatic catheterization (PTC).



ERCP image of hilar cholangiocarcinoma: Klatskin tumor with stricture of duct bifurcation (arrows)

From the collection of Dr Joseph Espat; used with permission



ERCP image of hepatic duct cholangiocarcinoma with duct stricture (arrows)

From the collection of Dr Joseph Espat; used with permission

The procedure of choice in further evaluating a cholangiocarcinoma is dependent on the need for biliary decompression.[34] ERCP is both diagnostic and therapeutic (procedures such as biopsy and decompressive stent placement can be performed, and brushings can be taken to acquire samples for cytologic and immunohistochemical examination).[35] However, it also requires the ability to cannulate the ampulla of Vater. If cannulation of the ampulla is not possible and biliary drainage is needed, then PTC is the treatment of choice. MRCP is the recommended procedure if only anatomic visualization of the bile ducts distal to the stricture is required. The use of ERCP does not exclude MRCP. EUS allows examination of the extrahepatic bile duct and tissue acquisition by fine needle aspiration from the primary mass and lymph nodes.[7] There is currently no consensus in the literature with regard to choosing between these interventions.

ERCP is an endoscopic procedure. The endoscope is introduced into the second part of the duodenum, and contrast dye is injected into the bile ducts. If a tumor is present, a filling defect or area of narrowing will be seen on the x-ray. During the procedure, samples of the tumor can be taken by brush or biopsy. These should be sent to pathology for diagnosis. A bile sample can be sent for cytologic analysis. The American Society for Gastrointestinal Endoscopy suggests using fluoroscopic-guided biopsy sampling

in combination with brush cytology in patients with biliary strictures of undetermined etiology undergoing ERCP.[36] An ERCP also allows stent insertion for palliative purposes. The risks of ERCP include those associated with sedation, damage or perforation of the gut wall, bleeding, allergic reaction to the dye, and pancreatitis. Endoscopists performing such procedures should be aware of associated adverse-event rates and their risk factors to optimize the informed consent process and patient selection.[37]

MRCP can enable evaluation of the biliary tree proximal and distal to an obstruction. It can therefore provide the surgeon with valuable information, such as if there is local invasion of the surrounding structures by the tumor. MRCP has the advantage of being noninvasive and does not carry the risks that ERCP or PTC do. The main disadvantage of MRCP is that it is diagnostic only and no therapeutic options can be performed.

PTC is an invasive procedure that is used when the tumor causes complete obstruction of the biliary tree and ERCP is unable to assess the biliary tree proximal to the tumor. It is also the imaging modality of choice when the tumor is persistent or has recurred. If a tumor is found to be unresectable, a stent can be placed during the procedure for palliation purposes. A bile sample can be taken during the procedure and sent for cytologic analysis.[32] The risks of PTC are bleeding, infection, and temporary or permanent renal impairment. Endoscopic-ultrasound guided, or percutaneous, biopsies should be avoided in patients with perihilar cholangiocarcinoma who are potential transplant candidates, due to the risk of tumor dissemination.[7]

Positron emission tomography

Positron emission tomography (PET) is useful in the diagnosis of many cancers; however, current literature cautions against the use of PET for determining the malignant potential of primary liver cancers. Literature on PET more strongly supports the role of restaging of hepatobiliary malignancies and identifying metastatic disease.[7] [38]

Immunostaining

Cholangiocarcinoma can present as mixed with hepatocellular cancer. These tumors are more aggressive. Immunostaining of pathologic specimens to detect markers of hepatocellular carcinoma (e.g., GPC3, HSP70, and glutamine synthetase) or progenitor cell features (e.g., K19, EpCAM) is recommended to distinguish intrahepatic cholangiocarcinoma from mixed hepatocellular cholangiocarcinoma if this information will change management.

Emerging tests

Optical coherence tomography (OCT) involves the use of infrared light to obtain scans that can correlate with histology. Peroral cholangioscopy is currently in development for diagnostic imaging and for pathologic diagnosis. Duodenoscope-assisted cholangioscopy evaluates the inside of the bile duct using the duodenal approach, as would be used for a stent placement.

History and exam

Key diagnostic factors

painless jaundice (common)

- Occurs in around 90% of patients.[6]

weight loss (uncommon)

- Occurs in around 35% of patients.[39]

abdominal pain (uncommon)

- Approximately 35% of patients may experience abdominal pain.[39]

Other diagnostic factors

pruritus (uncommon)

- Occurs in approximately 26% of patients.[39]

triad of fever, jaundice, and right upper quadrant pain (uncommon)

- Features of acute cholangitis. Occurs in 10% of patients.[39]

palpable gallbladder (uncommon)

- Rare.

hepatomegaly (uncommon)

- Rare.

dark urine (uncommon)

- If obstructive jaundice is present.

pale stools (uncommon)

- If obstructive jaundice is present.

asymptomatic (uncommon)

- Intrahepatic cholangiocarcinoma may be an incidental finding and may be detected during surveillance imaging in patients with cirrhosis. One study reported that 28% of intrahepatic cholangiocarcinomas, and 4% of extrahepatic cholangiocarcinomas, presented incidentally.[40] Symptoms are typically associated with more advanced disease.[7]

Risk factors

Strong

age >50 years

- Approximately two-thirds of cholangiocarcinomas occur in patients ages between 50 and 70 years.[4]

cholangitis

- Cholangitis increases the likelihood of intrahepatic cholangiocarcinoma, with an adjusted odds ratio (OR) of 8.8 and 95% confidence interval (CI) of 4.9 to 16.0.[9] [13]
- Although, historically, cholangitis has been related to an increased risk of extrahepatic cholangiocarcinoma, data are lacking on the strength of this association.

choledocholithiasis

- Choledocholithiasis increases the risk of intrahepatic cholangiocarcinoma, with an adjusted OR of 4.0, 95% CI of 1.9 to 8.5.[13]
- Limited data are available with regard to the association with extrahepatic cholangiocarcinoma, but a historic association exists.

cholecystolithiasis

- Cholecystolithiasis increases the risk of intrahepatic cholangiocarcinoma, with an OR of 4.0, 95% CI of 2.0 to 7.99.[9]
- Limited data are available with regard to the association with extrahepatic cholangiocarcinoma, but a historic association exists.

other structural disorders of the biliary tract

- Examples include bile duct adenoma, biliary papillomatosis, choledochal cyst, and Caroli disease (nonobstructive dilation of the biliary tract).[8] [21]

ulcerative colitis (UC)

- UC increases the risk of intrahepatic cholangiocarcinoma, with an OR of 2.3, 95% CI of 1.4 to 3.8.[13]
- Data are lacking with regard to the association with extrahepatic cholangiocarcinoma, but a historic association exists.

primary sclerosing cholangitis (PSC)

- PSC has been associated with high risk of cholangiocarcinoma, with its prevalence in patients with PSC ranging from 7% to 13%.[14] The risk of cholangiocarcinoma in patients with PSC increases with older age.[7] PSC also has a strong association with UC, another risk factor of cholangiocarcinoma; between 60% and 80% of all patients with PSC have a coexisting UC. The incidence of cholangiocarcinoma may be higher in patients with both conditions.[22] The American Association for the Study of Liver Diseases recommends that cholangiocarcinoma surveillance should be performed annually in adult patients with PSC (although not in those with small-duct PSC).[7]

nonspecific cirrhosis

- Nonspecific cirrhosis has a stronger association with intrahepatic cholangiocarcinoma, with an OR of 27.2, 95% CI of 19.9 to 37.1.[13]

alcoholic liver disease

- Alcoholic liver disease increases the risk of intrahepatic cholangiocarcinoma, with an OR of 7.4, 95% CI of 4.3 to 12.8.[13]
- Heavy drinking (>80 g of ethanol per day) has a strong association with intrahepatic cholangiocarcinoma (OR of 6.0, 95% CI of 2.3 to 16.7) and extrahepatic cholangiocarcinoma (OR of 4.0, 95% CI of 1.7 to 10.2).[23]

liver fluke infection

- *Clonorchis sinensis* increases the risk of intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma, with a relative risk (RR) of 2.7, 95% CI of 1.1 to 6.3.[10]
- *Clonorchis sinensis* and *Opisthorchis viverrini* infestation have been related in East Asian countries with higher incidence of cholangiocarcinoma; the activation of the host immune system and the chronic inflammatory state are proposed as the initial factors in the epithelial transformation to cancer.

chronic typhoid carrier

- In South-East Asia, where incidence of cholangiocarcinoma is increased, chronic typhoid carriers have a sixfold risk of developing a hepatobiliary malignancy.[24]

hepatitis C virus (HCV)

- HCV infection has a strong association with intrahepatic cholangiocarcinoma. In one study, the association showed an OR of 6.1, 95% CI of 4.3 to 8.6, while no association was found with extrahepatic cholangiocarcinoma, with an OR of 4.5, 95% CI of 0.8 to 45.7.[13]

HIV

- HIV infection has been related to intrahepatic cholangiocarcinoma, with an OR of 5.9, 95% CI of 1.8 to 18.8.[13] HIV infection is known to increase the prevalence of cholangitis either directly or via other opportunistic infections (e.g., cytomegalovirus).[25]
- HIV-related cholangitis could lead to changes similar to those induced by other inflammatory conditions of the bile duct that eventually result in cancer; it could be a confounding factor because HIV tends to co-occur with HCV infection.

hepatitis B virus (HBV)

- HBV-infected patients have been found to have a higher prevalence of intrahepatic cholangiocarcinoma in several studies.[10] [26] [27]
- Other studies have not found any association between intrahepatic cholangiocarcinoma and HBV infections; however, the number of patients studied was small.[13]

exposure to thorium dioxide

- Exposure to thorium dioxide, such as thorotrast, a radioactive contrast agent used until the 1950s, results in an increased incidence of cholangiocarcinoma.[18]

Weak

diabetes

- No clear association has been found.[9] [13]

cigarette smoking

- No clear association has been found.[9] [13] Smoking may increase the risk of cholangiocarcinoma in patients with PSC.[28]

exposure to toxins/medications

- Occupational exposure to polychlorinated biphenyls (PCBs), isoniazid, oral contraceptive pills, and chronic typhoid carriers poses an increased risk of cholangiocarcinoma.[15] [16] [17] [29]

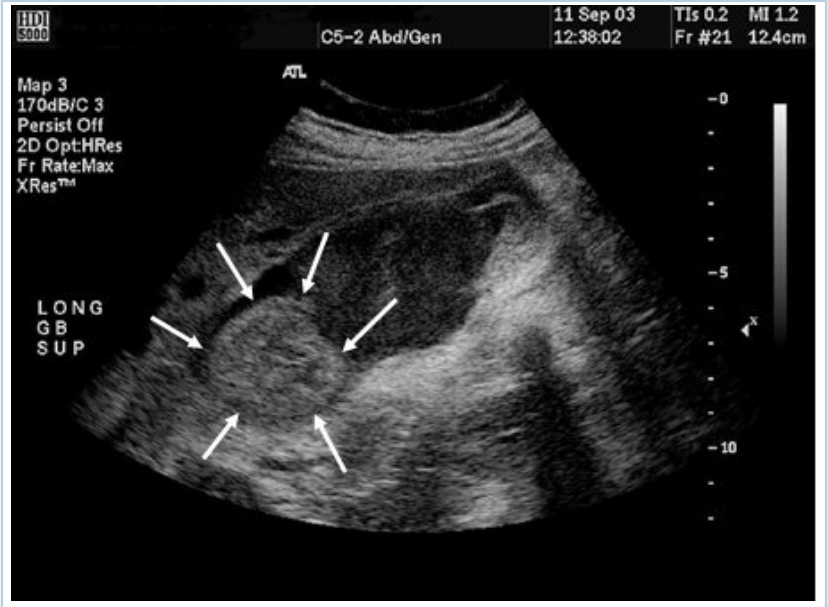
male sex

- There is a slight male predominance.[4]

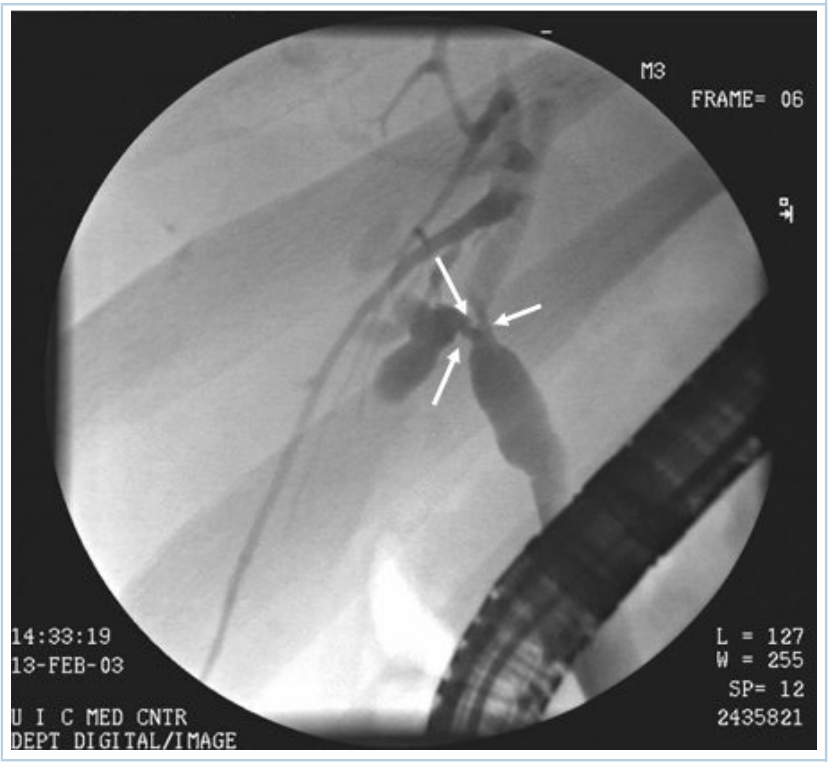
Tests

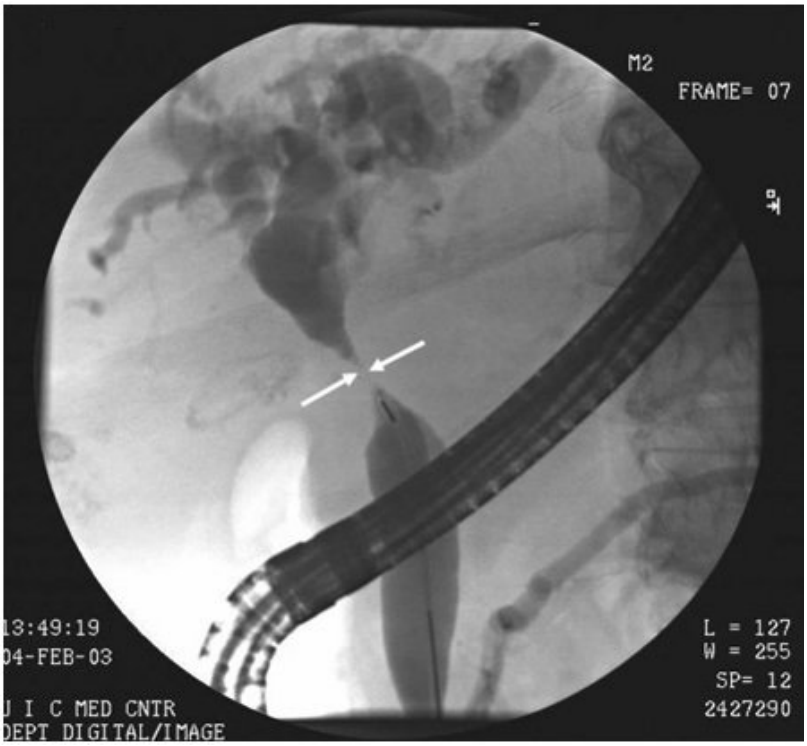
1st test to order

Test	Result
serum bilirubin • Conjugated bilirubin is elevated in obstructive jaundice.	**elevated**
serum alkaline phosphatase • Suggests obstructive (or cholestatic) pattern of elevated LFTs.	**elevated**
serum gamma-GT • Suggests obstructive (or cholestatic) pattern of elevated LFTs.	**elevated**
serum aminotransferase • May be minimally elevated. High elevations are seen more frequently in intrahepatic cholangiocarcinoma with direct hepatic invasion.[30]	**elevated**
serum prothrombin time • Caused by prolonged obstruction of the common bile or hepatic duct and a subsequent reduction in fat-soluble vitamins (A, D, E, and K).	**increased**
serum CA 19-9 • Elevated in up to 85% of patients with cholangiocarcinoma. Also elevated in pancreatic or gastric malignancy, in severe hepatic injury from any cause, and with obstructive jaundice without malignancy. However, if levels continue to be elevated after biliary decompression, this suggests malignancy. Significantly elevated levels (>1000 U/mL) may indicate presence of metastatic disease.[7] [41] In patients with primary sclerosing cholangitis and suspected cholangiocarcinoma, a value of >100 units/mL has a sensitivity of 75% and specificity of 80%.[42]	**elevated**
serum carcinoembryonic antigen (CEA) • Also elevated in inflammatory bowel disease, other tumors, and severe liver injury.	**elevated**
serum CA-125 • Detectable in up to 65% of patients.	**elevated**
abdominal ultrasound • Identifies malignant versus benign lesions with a sensitivity of 92% and a specificity of 93%.[43]	**diagnosis suspected when intrahepatic ducts are dilated; intrahepatic cholangiocarcinoma may be seen as a mass lesion**

Test	Result
 *Gallbladder ultrasound of mass (arrows)* *From the collection of Dr Joseph Espat; used with permission*	
abdominal CT • CT identifies a primary lesion in approximately 59% of patients.[44] Cross-sectional imaging of the liver with CT or MRI is essential for evaluation of the primary mass, presence of metastases, vascular invasion, and resectability.[7] [34]	**intrahepatic mass lesion, dilated intrahepatic ducts, and localized lymphadenopathy may be seen**
abdominal MRI • MRI is often utilized to differentiate between solid and cystic biliary contents. Furthermore, MRI can provide additional information regarding tumor size, extent of bile duct involvement, vascular patency, extrahepatic extension, nodal or distant metastases, and the presence of lobar atrophy. MRI diagnostic performance is comparable to CT.[33] Cross-sectional imaging of the liver with CT or MRI is essential for evaluation of the primary mass, presence of metastases, vascular invasion, and resectability.[7] [34]	**local extent of tumor (the tumor is hypointense in T1- and hyperintense in T2-weighted image), hepatic parenchymal abnormalities, and liver metastases can be seen**

Other tests to consider

Test	Result
endoscopic ultrasound (EUS) • EUS allows examination of the extrahepatic bile duct and tissue acquisition by fine needle aspiration from the primary mass and lymph nodes.[7] Endoscopic-ultrasound guided, or percutaneous, biopsies should be avoided in patients with perihilar cholangiocarcinoma who are potential transplant candidates, due to the risk of tumor dissemination.[7]	**characterizes size and location of tumor**
MR angiography • Preoperative imaging with MR angiography is a noninvasive method for staging cholangiocarcinoma, and therefore also helps determine resectability.	**staging tool**
ERCP • Tissue diagnosis in 40% to 70%.  *ERCP image of hilar cholangiocarcinoma: Klatskin tumor with stricture of duct bifurcation (arrows)* *From the collection of Dr Joseph Espat; used with permission*	**a filling defect or area of narrowing will be seen if a tumor is present**

Test	Result
 *ERCP image of hepatic duct cholangiocarcinoma with duct stricture (arrows)* *From the collection of Dr Joseph Espat; used with permission* • Staining for carcinoembryonic antigen (CEA), CA 19-9, or CA-50 aids in making a pathologic diagnosis.[6] [9] [14] [20]	
MRCP • Sensitivity comparable to PTC.[45] MRCP has the advantage of being noninvasive and does not carry the risks that ERCP or PTC do. The main disadvantage of MRCP is that it is diagnostic only, and no therapeutic options can be performed.	**can show extent of duct involvement above and below the obstruction**
percutaneous transhepatic catheterization (PTC) • Diagnostic sensitivity as high as 92%.[46] An invasive procedure that is used when the tumor causes complete obstruction of the biliary tree, and ERCP is unable to assess the biliary tree proximal to the tumor.	**may show dilated intrahepatic ducts with irregular filling defects and strictures at site of occlusion**
positron emission tomography (PET) • PET is useful in the diagnosis of many cancers; however, current literature cautions against the use of PET for determining the malignant potential of primary liver cancers. Literature on PET more strongly supports the role of restaging hepatobiliary malignancies and identifying metastatic disease.[7] [38] • Sensitivity is low in cholangiocarcinoma.	**evidence of malignancy**
Immunostaining • Immunostaining of pathologic specimens to detect markers of hepatocellular carcinoma (e.g., GPC3, HSP70, and glutamine synthetase) or progenitor cell features (e.g., K19, EpCAM) is recommended to distinguish intrahepatic cholangiocarcinoma from	**may help to distinguish intrahepatic cholangiocarcinoma from mixed hepatocellular cholangiocarcinoma**

Test	Result
mixed hepatocellular-cholangiocarcinoma tumors if this information will change management.	

Emerging tests

Test	Result
optical coherence tomography (OCT) • Infrared light used to obtain scans that can correlate with histology.	**variable**
peroral cholangioscopy • In development for diagnostic imaging and for pathologic diagnosis.	**variable**
duodenoscope-assisted cholangioscopy • Evaluates the inside of the bile duct using the duodenal approach, as would be used for a stent placement. The FDA recommends duodenoscopes that have disposable, rather than fixed, endcaps to help limit device contamination.	**variable**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Hepatocellular carcinoma (HCC)	• Patients generally present with symptoms of advancing cirrhosis, with jaundice, ascites, asterixis, pedal edema, periumbilical collateral veins, and possibly alcoholic stigmata. There may be a history of variceal bleeding and episodes of hepatic encephalopathy.	• The same imaging modalities are used. • HCC is the more likely diagnosis if the lesion is peripheral and cirrhotic parenchyma is present, but ultimately it will be pathology that distinguishes between the two tumors.
Ampullary carcinoma	• Presents with many of the same features as cholangiocarcinoma, with jaundice, pruritus, anorexia, weight loss, and a distended, palpable gallbladder. • Patients may have diarrhea, which is not commonly associated with cholangiocarcinoma.	• Diagnosis of ampullary lesion is made using ERCP; however, confirmation of malignancy requires histologic examination.
Pancreatic carcinoma	• A characteristic feature is significant weight loss. Patients may also experience epigastric or back pain, which is not commonly seen with cholangiocarcinoma.	• The same imaging modalities are used. It may be clear from CT or MRI that the tumor is arising from the body of the pancreas, but more difficult to distinguish if the tumor is arising from the head of the pancreas. Ultimately it is the histology that will distinguish between the two tumors.
Choledocholithiasis	• Gallstones in the common bile duct (CBD) can present with signs and symptoms of obstructive jaundice. In addition, the presence of gallstones in the CBD and cystic duct obstruction can mimic Courvoisier sign (presents with enlarged gallbladder, which would be similar to an obstruction secondary to tumor in the bile duct). Gallstones in the gallbladder can cause no symptoms.	• ERCP will definitively diagnose and treat this condition.

Condition	Differentiating signs / symptoms	Differentiating tests
Cholangitis	• This typically presents as a triad of fever, right upper quadrant pain, and jaundice. • Although a common cause for the infection can be gallstones in the CBD, the infection can also be superimposed upon obstruction caused by a tumor.	• Clinical diagnosis of a consequence of biliary obstruction regardless of cause. • WBC count is elevated and imaging (CT, MRCP, ERCP) demonstrates biliary obstruction. • Blood cultures may be positive for etiologic organism.

Criteria

American Joint Committee on Cancer TNM staging system (8th Edition)[1]

The American Joint Committee on Cancer (AJCC) staging system describes the extent of disease based on the following anatomic factors: size and extent of the primary tumor (T); regional lymph node involvement (N); and presence or absence of distant metastases (M). Nonanatomic prognostic factors (e.g., tumor grade, biomarkers) may be used to supplement the staging of certain cancers. Staging laparoscopy is also performed to determine the presence of peritoneal or superficial liver metastases in patients who have potentially resectable disease.[47]

Approach

General approach

It is recommended that management of a patient with cholangiocarcinoma be carried out by a multidisciplinary team consisting of specialist surgeons, radiologists, oncologists, and palliative care specialists. Referral to a center with expertise in hepatobiliary malignancies is desirable.[7]

Surgical resection is the only potential cure, but only a small percentage of patients are successfully treated this way. Other options include liver transplant (although only a few select patients qualify for this), chemotherapy, immunotherapy, and/or radiation and palliation.

Although management for intrahepatic and extrahepatic cholangiocarcinoma does differ, patients generally can be divided into those who have resectable tumors and those who do not.

Resectable tumors

Patients who have resectable tumors have:

- No evidence of metastases, regional lymph node involvement, portal vein extension, or bilateral ductal extension
- Sufficient functional liver volume[7]
- Imaging indicating the possibility that the surgeon will be able to resect with clear margins and be able to clear at least one side of the biliary tree of tumor
- No comorbidities that prevent the patient from undergoing surgery.

The goal of surgery is to achieve negative margins (there is a 20% to 43% 5-year survival rate if this occurs).[50] [51] [52] [53] Positive predictors of survival are negative margins, absence of lymph node involvement, solitary lesions, and lack of vascular invasion. Hilar involvement lowers medial survival to 12 to 24 months, from 18 to 30 months for more distal tumors.

Adjuvant therapies after radical resection have been shown in one meta-analysis to increase overall survival and disease-free survival compared to observation alone, and should be considered for eligible patients.[54] However, the authors noted a lack of head-to-head studies between adjuvant chemotherapy, radiation therapy, or chemoradiation therapy.

Intrahepatic tumors

- Patients with a resectable intrahepatic cholangiocarcinoma should undergo a partial liver resection.[34] [48]
- If resection is successful and there is no local residual disease, patients can be followed up by observation, enrolled in a clinical trial, or offered chemotherapy.[34] [48]
- Based on evidence from one phase 3 randomized controlled trial, the American Society of Clinical Oncology, the US National Comprehensive Cancer Network (NCCN), and the American Association for the Study of Liver Diseases (AASLD) recommend adjuvant capecitabine chemotherapy for a duration of 6 months for all patients following resection.[7] [34] [48] [55] [56]
- Furthermore, NCCN recommends treatment with durvalumab, in combination with gemcitabine and cisplatin, in patients who develop recurrent disease more than 6 months after surgery with curative intent and more than 6 months after completion of adjuvant therapy.[34] [48] [57]

- Durvalumab is a human IgG1 monoclonal antibody that binds with high affinity and specificity to the programmed cell death ligand 1 (PD-L1).[58] It is a potent antagonist of PD-L1 function, blocking interaction with PD-1 and CD80.[58]
- Its efficacy was evaluated in one phase 3, randomized, double-blind, placebo-controlled trial in patients with histologically confirmed unresectable, locally advanced, or metastatic biliary tract cancer, who had not previously received systemic therapy for advanced disease.[57] The trial showed that durvalumab plus chemotherapy significantly improved overall survival, compared with placebo plus chemotherapy.[57] [59] Addition of durvalumab to chemotherapy did not have detrimental effects on patient-related outcomes, and the combination can be considered a tolerable treatment regimen in patients with advanced biliary tract cancer.[60]

- Patients with high-risk features after resection, such as positive lymph nodes, may benefit from adjuvant radiation therapy with concurrent chemotherapy.[61]
- Staging laparoscopy may be considered in conjunction with surgery if no distant metastases are found.[34] [48]
- Thermal ablation can be used as an alternative to surgical resection in patients with high-risk disease with recurrent or primary small single tumors <3 cm.[34] [48]

Extrahepatic tumors

- For patients with an extrahepatic cholangiocarcinoma, the type of surgery depends on the location of the tumor:
  - Tumors that are within the proximal third of the extrahepatic biliary tree should be removed by hilar resection, partial hepatectomy combined with caudate lobe resection, and lymphadenectomy.[62]
  - Tumors within the mid-third should undergo major bile duct excision with lymphadenectomy. Either partial hepatectomy or pancreaticoduodenectomy may be required to achieve complete tumor clearance.
  - Distal extrahepatic tumors should be removed with pancreaticoduodenectomy with lymphadenectomy.
  - Tumors can be resected by portal vein resection when the portal vein is involved. This approach confers a marginal benefit over not undergoing resection.[63]
- If the tumor is resected successfully and there are no positive lymph nodes, the patient can be followed up by observation, enrolled in a clinical trial, or undergo chemotherapy with/without radiation.[34] [48] Treatment with adjuvant capecitabine chemotherapy for a duration of 6 months is recommended for all patients following resection.[7] [32][34] [48] [55]
- If resection margins are positive or lymph nodes are involved, the patient may be offered chemotherapy, either alone or in conjunction with radiation therapy.[34] [48] [55] [64] [65]
- Patients who develop recurrent disease more than 6 months after surgery with curative intent and more than 6 months after completion of adjuvant therapy may be offered immunotherapy in conjunction with chemotherapy (durvalumab, in combination with gemcitabine and cisplatin).[34] [48] [57]

Preoperative portal vein embolization may contribute to reduction of complications and surgery-related mortality, and may be considered for patients undergoing right hepatectomy or larger resection, such as trisegmentectomy.[66] [67] It may also be considered for patients undergoing hepatectomy with a planned resection rate exceeding 50% to 60%, especially those with a jaundiced liver.

Preoperative biliary drainage has been used to reduce morbidity and mortality in patients with obstructive jaundice. However, systematic reviews and meta-analyses have found no evidence of clinical benefit, and it remains a controversial procedure.[68] [69] [70] [71] Generally, preoperative biliary drainage is not required for patients with a resectable lesion when surgery can be performed within a few days of diagnosis. European Society of Gastrointestinal Endoscopy (ESGE) and the American College of Gastroenterology (ACG) guidelines recommend against routine preoperative biliary drainage specifically for patients with malignant extrahepatic biliary obstruction.[72] [73] ESGE and ACG guidelines also recommend that preoperative biliary drainage should be reserved for patients with cholangitis, severe symptomatic jaundice (e.g., intense pruritus), delayed surgery, or for before neoadjuvant chemotherapy in patients with jaundice.[72] [73] However, AASLD guidance notes that in patients undergoing resection for perihilar or distal cholangiocarcinoma, preoperative biliary drainage of the remnant liver is recommended if biliary obstruction is present.[7]

Unresectable tumors

Criteria that make a tumor unresectable are:[74]

Patient factors

- Comorbidity
- Coexistent hepatic cirrhosis.

Tumor-related factors

- Tumor extension to secondary biliary radicles
- Encasement or occlusion of main portal vein proximal to the bifurcation
- Atrophy of one hepatic lobe with contralateral portal vein branch encasement or occlusion
- Atrophy of one hepatic lobe with contralateral tumor extension to secondary biliary radicles
- Unilateral tumor extension to secondary biliary radicles with contralateral portal vein branch encasement or occlusion
- Histologically proven metastasis to regional lymph nodes
- Lung, liver, or peritoneal metastasis.

Liver transplant

- Results are mixed concerning liver transplant, but it can be supported in highly selected groups of patients with unresectable disease:
    - Patients with locally advanced disease (typically hilar) involving the surrounding large vessels (portal vein, hepatic artery), and extension to secondary biliary radicles
    - Patients with underlying biliary inflammation (e.g., primary sclerosing cholangitis) or hepatic dysfunction precluding surgery.[7] [75] [76] [77]
- Regional lymph node involvement and the presence of distant metastasis exclude the patient from liver transplant.
- Most high-volume centers performing this procedure use neoadjuvant chemotherapy or chemoradiation, with the thought that it will limit recurrence from metastasis and lymphatic spread.[78]

Chemotherapy ± immunotherapy ± radiation

- Each patient is considered on an individual basis, but patients who are not transplant candidates are typically offered chemotherapy with gemcitabine plus a platinum compound, either alone or in combination with radiation therapy.[7][64] [65] Upon progression on gemcitabine and platinum

chemotherapy, the combination of FOLFOX (leucovorin, fluorouracil, and oxaliplatin) may be an appropriate second line therapy.[7] [34] [48] [79] However, due to the limited response rate in this tumor, treatment may be discontinued if progression of disease is confirmed by imaging. A number of tumors that are downstaged may be considered resectable post chemoradiation.[80]

- In patients with unresectable cholangiocarcinoma, transarterial chemotherapy-based treatment may confer a survival benefit of 2-7 months compared with systemic therapy.[81]
- NCCN guidelines recommend that durvalumab or pembrolizumab, in combination with gemcitabine and cisplatin, should be considered for the primary treatment of patients with unresectable and metastatic biliary tract cancers.[34] [48] [57] [82]
- The National Institute for Health and Care Excellence (NICE) in the UK recommends durvalumab in combination with gemcitabine and cisplatin as an option for the treatment of patients with unresectable, locally advanced, or metastatic biliary tract cancers.[83]
- Chemotherapy may be combined with chemoradiation.[34] [48]
- Next generation sequencing should be considered to try to identify relevant targetable genetic alterations in the patient to further guide second-line treatment options.[7]
- Patients should be considered for inclusion in clinical trials.[34] [48]

Palliative therapy

- The alternative option for unresectable tumors is palliative care. The goal of palliation is symptom resolution and enhanced quality of life. Biliary obstruction is the most common complication when a tumor is unresectable or a patient is not suitable for surgery. Options for relieving biliary obstruction include surgical bypass, endoscopic biliary stenting, and percutaneous biliary drainage. Surgical biliary bypass is associated with the most morbidity and mortality.
- Locoregional therapy or liver-directed therapeutic options (broadly categorized into ablation, arterially directed therapies, and radiation therapy) may be considered for liver-limited, locally-advanced unresectable intrahepatic cholangiocarcinoma.[7] [34] [48]
- Ablation options include cryoablation, photodynamic therapy, radiofrequency ablation, microwave ablation, and irreversible electroporation.[34] [48]
- Arterially directed therapies include transarterial embolization, transarterial chemoembolization, transarterial chemoembolization with drug-eluting beads, and yttrium 90.[34] [48] Patients with limited extrahepatic disease (hilar lymph node ≤3 cm or ≤5 lung nodules each ≤1 cm) may be considered for arterially directed therapy in combination with systemic therapy.[34] [48]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
resectable disease		
intrahepatic tumor	1st	partial liver resection
	adjunct	preoperative portal vein embolization or biliary drainage
	adjunct	chemotherapy ± immunotherapy ± radiation
extrahepatic tumor	1st	surgical excision
	adjunct	preoperative portal vein embolization or biliary drainage
	adjunct	chemotherapy ± immunotherapy ± radiation
unresectable disease		
liver transplant candidate	1st	liver transplant
	plus	chemotherapy ± radiation
liver transplant non-candidate	1st	chemotherapy ± immunotherapy ± radiation
	1st	palliative therapy

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

resectable disease

intrahepatic tumor

1st **partial liver resection**

» Patients who have resectable tumors have: no evidence of metastases, regional lymph node involvement, portal vein extension, or bilateral ductal extension, and sufficient functional liver volume; imaging indicating the possibility that the surgeon will be able to resect with clear margins and be able to clear at least one side of the biliary tree of tumor; no comorbidities that prevent them from undergoing surgery.[7]

» The goal of surgery is to achieve negative margins (there is a 20% to 43% 5-year survival rate if this occurs).[50] [51] [52] [53] Positive predictors of survival are negative margins, absence of lymph node involvement, solitary lesions, and lack of vascular invasion. Hilar involvement lowers medial survival to 12 to 24 months, from 18 to 30 months for more distal tumors. Staging laparoscopy may be considered in conjunction with surgery if no distant metastases are found.[34] [48] In patients with high-risk disease with recurrent or primary small single tumors <3 cm, thermal ablation can be used as an alternative to surgical resection.[34] [48]

adjunct **preoperative portal vein embolization or biliary drainage**

Treatment recommended for SOME patients in selected patient group

» Preoperative portal vein embolization may contribute to reduction of complications and surgery-related mortality, and may be considered for patients undergoing right hepatectomy or larger resection, such as trisegmentectomy.[66] [67] It may also be considered for patients undergoing hepatectomy with a planned resection rate exceeding 50% to 60%, especially those with a jaundiced liver.

» Preoperative biliary drainage has been used to reduce morbidity and mortality in patients with obstructive jaundice. However, systematic reviews and meta-analyses have found no evidence of clinical benefit, and it remains a controversial procedure.[68] [69] [70] [71]

Acute

Generally, preoperative biliary drainage is not required for patients with a resectable lesion when surgery can be performed within a few days of diagnosis. European Society of Gastrointestinal Endoscopy (ESGE) and the American College of Gastroenterology (ACG) guidelines recommend against routine preoperative biliary drainage specifically for patients with malignant extrahepatic biliary obstruction.[72] [73] ESGE and ACG guidelines also recommend that preoperative biliary drainage should be reserved for patients with cholangitis, severe symptomatic jaundice (e.g., intense pruritus), delayed surgery, or for before neoadjuvant chemotherapy in patients with jaundice.[72] [73] However, American Association for the Study of Liver Diseases (AASLD) guidance notes that in patients undergoing resection for perihilar or distal cholangiocarcinoma, preoperative biliary drainage of the remnant liver is recommended if biliary obstruction is present.[7]

adjunct **chemotherapy ± immunotherapy ± radiation**

Treatment recommended for SOME patients in selected patient group

» If resection is successful and there is no local residual disease, patients can be followed up by observation, enrolled in a clinical trial, or offered chemotherapy.[34] [48] Based on evidence from one phase 3 randomized controlled trial, the American Society of Clinical Oncology, the US National Comprehensive Cancer Network (NCCN), and the American Association for the Study of Liver Diseases (AASLD), recommend adjuvant capecitabine chemotherapy for a duration of 6 months for all patients following resection.[7] [34][48] [55] [56]

» Furthermore, NCCN recommends treatment with durvalumab, in combination with gemcitabine and cisplatin, in patients who develop recurrent disease more than 6 months after surgery with curative intent and more than 6 months after completion of adjuvant therapy.[34] [48] [57] Patients with high-risk features after resection, such as positive lymph nodes, may benefit from adjuvant radiation therapy with concurrent chemotherapy.[61]

» See local specialist protocol for dosing guidelines of chemotherapeutic agents.

extrahepatic tumor **1st** **surgical excision**

Acute

» Patients who have resectable tumors have: no evidence of metastases, regional lymph node involvement, portal vein extension, or bilateral ductal extension, and sufficient functional liver volume; imaging indicating the possibility that the surgeon will be able to resect with clear margins and be able to clear at least one side of the biliary tree of tumor; no comorbidities that prevent them from undergoing surgery.[7]

» For patients with an extrahepatic cholangiocarcinoma, the type of surgery depends on the location of the tumor:

» Tumors that are within the proximal third of the extrahepatic biliary tree should be removed by hilar resection, partial hepatectomy combined with caudate lobe resection, and lymphadenectomy.[62]

» Tumors within the mid-third should undergo major bile duct excision with lymphadenectomy. Either partial hepatectomy or pancreaticoduodenectomy may be required to achieve complete tumor clearance.

» Distal extrahepatic tumors should be removed with pancreaticoduodenectomy with lymphadenectomy.

» Tumors can be resected by portal vein resection when the portal vein is involved. This approach confers a marginal benefit over not undergoing resection.[63]

adjunct **preoperative portal vein embolization or biliary drainage**

Treatment recommended for SOME patients in selected patient group

» Preoperative portal vein embolization may contribute to reduction of complications and surgery-related mortality, and may be considered for patients undergoing right hepatectomy or larger resection, such as trisegmentectomy.[66] [67] It may also be considered for patients undergoing hepatectomy with a planned resection rate exceeding 50% to 60%, especially those with a jaundiced liver.

» Preoperative biliary drainage has been used to reduce morbidity and mortality in patients with obstructive jaundice. However, systematic reviews and meta-analyses have found no evidence of clinical benefit, and it remains a controversial procedure.[68] [69] [70] [71] Generally, preoperative biliary drainage is not required for patients with a resectable

Acute

lesion when surgery can be performed within a few days of diagnosis. European Society of Gastrointestinal Endoscopy (ESGE) and the American College of Gastroenterology (ACG) guidelines recommend against routine preoperative biliary drainage specifically for patients with malignant extrahepatic biliary obstruction.[72] [73] ESGE and ACG guidelines also recommend that preoperative biliary drainage should be reserved for patients with cholangitis, severe symptomatic jaundice (e.g., intense pruritus), delayed surgery, or for before neoadjuvant chemotherapy in patients with jaundice.[72] [73] However, AASLD guidance notes that in patients undergoing resection for perihilar or distal cholangiocarcinoma, preoperative biliary drainage of the remnant liver is recommended if biliary obstruction is present.[7]

adjunct **chemotherapy ± immunotherapy ± radiation**

Treatment recommended for SOME patients in selected patient group

» If the tumor is resected successfully and there are no positive lymph nodes, the patient can be followed up by observation, enrolled in a clinical trial, or undergo chemotherapy with/without radiation.[34] [48] Treatment with adjuvant capecitabine chemotherapy for a duration of 6 months is recommended for all patients following resection.[7] [34] [48] [55]

» If resection margins are positive or lymph nodes are involved, the patient may be offered chemotherapy, either alone or in combination with radiation therapy.[34] [48] [55] [64] [65]

» Patients who develop recurrent disease more than 6 months after surgery with curative intent and more than 6 months after completion of adjuvant therapy may be offered immunotherapy in conjunction with chemotherapy (durvalumab, in combination with gemcitabine and cisplatin).[34] [48] [57]

» See local specialist protocol for dosing guidelines of chemotherapeutic agents.

unresectable disease

liver transplant candidate **1st** **liver transplant**

» Most cholangiocarcinomas present as unresectable. Criteria that make a tumor unresectable are:[74]

Acute

» Patient factors: comorbidity; coexistent hepatic cirrhosis.

» Tumor-related factors: tumor extension to secondary biliary radicles; encasement or occlusion of main portal vein proximal to the bifurcation; atrophy of one hepatic lobe with contralateral portal vein branch encasement or occlusion; atrophy of one hepatic lobe with contralateral tumor extension to secondary biliary radicles; unilateral tumor extension to secondary biliary radicles with contralateral portal vein branch encasement or occlusion; histologically proven metastasis to regional lymph nodes; lung, liver, or peritoneal metastasis.

» Results are mixed concerning liver transplant, but it can be supported in highly selected groups of patients with unresectable disease. They include patients with locally advanced disease (typically hilar) involving the surrounding large vessels (portal vein, hepatic artery) and extension to secondary biliary radicles. Patients with underlying biliary inflammation (e.g., primary sclerosing cholangitis) or hepatic dysfunction precluding surgery may also qualify for liver transplant.[7] [75] [76] [77] Regional lymph node involvement and the presence of distant metastasis exclude the patient from transplant.

plus **chemotherapy ± radiation**

Treatment recommended for ALL patients in selected patient group

» Most high-volume centers performing liver transplant use neoadjuvant chemotherapy or chemoradiation, with the thought that it will limit recurrence from metastasis and lymphatic spread.[78]

liver transplant non-candidate **1st** **chemotherapy ± immunotherapy ± radiation**

» Most cholangiocarcinomas present as unresectable. Criteria that make a tumor unresectable are:[74]

» Patient factors: comorbidity; coexistent hepatic cirrhosis.

» Tumor-related factors: tumor extension to secondary biliary radicles; encasement or occlusion of main portal vein proximal to the bifurcation; atrophy of one hepatic lobe with contralateral portal vein branch encasement or occlusion; atrophy of one hepatic lobe with contralateral tumor extension

Acute

to secondary biliary radicles; unilateral tumor extension to secondary biliary radicles with contralateral portal vein branch encasement or occlusion; histologically proven metastasis to regional lymph nodes; lung, liver, or peritoneal metastasis.

» Within the group of patients who have unresectable disease, only a small number qualify for a liver transplant. They include patients with locally advanced disease involving the surrounding large vessels (portal vein, hepatic artery) and extension to secondary biliary radicles. Patients with underlying biliary inflammation (e.g., primary sclerosing cholangitis) or hepatic dysfunction precluding surgery may also qualify for liver transplant.[7] [75] [76] [77]

» Each patient is considered on an individual basis. Patients who do not meet the above criteria are typically offered chemotherapy with gemcitabine plus a platinum compound, either alone or in combination with radiation therapy.[7] [64] [65] Upon progression on gemcitabine and platinum chemotherapy, the combination of FOLFOX (leucovorin, fluorouracil, and oxaliplatin) may be an appropriate second line therapy.[7] [34] [48] [79] However, due to the limited response rate in this tumor, treatment may be discontinued if progression of disease is confirmed by imaging. A number of tumors that are downstaged may be considered resectable post chemoradiation.[80] In patients with unresectable cholangiocarcinoma, transarterial chemotherapy-based treatment may confer a survival benefit of 2-7 months compared with systemic therapy.[81]

» NCCN guidelines recommend that durvalumab or pembrolizumab, in combination with gemcitabine and cisplatin, should be considered for the primary treatment of patients with unresectable and metastatic biliary tract cancers.[34][48] [57] [82] The National Institute for Health and Care Excellence (NICE) in the UK recommends durvalumab in combination with gemcitabine and cisplatin as an option for the treatment of patients with unresectable, locally advanced, or metastatic biliary tract cancers.[83]

» Chemotherapy may be combined with chemoradiation.[34] [48]

» Next generation sequencing should be considered to try to identify relevant targetable genetic alterations in the patient to further guide second-line treatment options.[7] Patients should

Acute

be considered for inclusion in clinical trials.[34] [48]

» See local specialist protocol for dosing guidelines of chemotherapeutic agents.

1st **palliative therapy**

» The alternative option for unresectable tumors is palliative care. The goal of palliation is symptom resolution and enhanced quality of life. Biliary obstruction is the most common complication when a tumor is unresectable or a patient is not suitable for surgery. Options for relieving biliary obstruction include surgical bypass, endoscopic biliary stenting, and percutaneous biliary drainage. Surgical biliary bypass is associated with the most procedural-associated morbidity and mortality.

» Locoregional therapy or liver-directed therapeutic options (broadly categorized into ablation, arterially directed therapies, and radiation therapy) may be considered for liver-limited, locally-advanced unresectable intrahepatic cholangiocarcinoma.[7] [34] [48] Ablation options include cryoablation, photodynamic therapy, radiofrequency ablation, microwave ablation, and irreversible electroporation.[34] [48] Arterially directed therapies include transarterial embolization, transarterial chemoembolization, transarterial chemoembolization with drug-eluting beads, and yttrium 90.[34] [48] Patients with limited extrahepatic disease (hilar lymph node ≤3 cm or ≤5 lung nodules each ≤1 cm) may be considered for arterially directed therapy in combination with systemic therapy.[34] [48]

Emerging

Selective internal radiation therapy

Selective internal radiation therapy (SIRT) or radioembolization, targets high doses of radiation directly to unresectable liver metastases. The National Institute for Health and Care Excellence (NICE) in the UK has published guidance for the use of SIRT for unresectable primary intrahepatic cholangiocarcinoma. NICE recommends that the procedure should be carried out in specialist centers and only in the context of research, due to safety concerns and the lack of good quality evidence for its efficacy.[84]

Devimistat

Devimistat, an experimental antimitochondrial drug that targets the mitochondrial tricarboxylic acid cycle, has been granted orphan drug status by the Food and Drug Administration (FDA) for the treatment of biliary cancer. A phase 1B/2 trial of devimistat in combination with gemcitabine and cisplatin for patients with biliary cancer is ongoing.[85]

Etoposide toniribate

The FDA and European Medicines Agency (EMA) have granted orphan drug designation to the novel topoisomerase II inhibitor, etoposide toniribate, for the treatment of relapsed refractory cholangiocarcinoma. One randomized phase 2 trial of patients with relapsed refractory, metastatic, unresectable biliary tract cancer (n=22) reported a 1-year overall survival of 44% with etoposide toniribate versus 11% with best supportive care.[86]

Infigratinib

Infigratinib, an oral, small molecule kinase inhibitor of fibroblast growth factor receptor (FGFR), has been granted accelerated approval by the FDA for adults with previously treated, unresectable locally, advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptors 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test. The approval was premised on the results of one multicenter, open-label, single-arm, phase 2 study.[87] In October 2022, the application to the EMA for marketing authorization for infigratinib was withdrawn. This followed the initial EMA evaluation that there was insufficient evidence of efficacy, as well as a number of severe side effects and questions over metabolism and excretion, that suggested the benefits of infigratinib did not outweigh its risks.

Futibatinib

Futibatinib, an oral, highly selective and irreversible small molecule inhibitor of FGFR types 1 to 4, has received approval from the FDA for patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring FGFR2 gene rearrangements, including gene fusions. Futibatinib is also approved by the EMA for patients with locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy. One phase 2 trial reported a measurable clinical benefit with futibatinib in patients with unresectable or metastatic FGFR2 fusion-positive or FGFR2 rearrangement-positive intrahepatic cholangiocarcinoma and disease progression after one or more previous lines of systemic therapy (excluding FGFR inhibitors).[88] One phase 3 trial (FOENIX-CCA3) is in progress.[89]

Gunagratinib

Gunagratinib, a pan-FGFR inhibitor, has been granted orphan drug status by the FDA for the treatment of cholangiocarcinoma. Anti-tumor activity was demonstrated in patients with FGF/FGFR gene aberrations in multiple tumor types, including cholangiocarcinoma.[90] One phase 2A dose expansion study is ongoing.[91] [92]

Ivosidenib

Ivosidenib, an oral, small molecule inhibitor of isocitrate dehydrogenase-1 (IDH1), has been approved by the FDA and EMA for the treatment of adults with previously treated, locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation as detected by an approved test. In patients with previously treated IDH1-mutant cholangiocarcinoma, progression-free survival was significantly improved with ivosidenib compared with placebo (median 2.7 months vs 1.4 months).[93] Median overall survival, a secondary end point, was 10.3 months with ivosidenib versus 7.5 months with placebo.[94] When adjusted for crossover from placebo to ivosidenib (permitted if patients had disease progression), median overall survival with placebo was 5.1 months. The NCCN recommends ivosidenib as a subsequent line treatment which is useful in some circumstances for patients with unresectable or metastatic cholangiocarcinoma with IDH1 mutations following disease progression.[34] [48] NICE recommends ivosidenib as an option for treating locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation in adults after one or more systemic treatments.[95]

Pemigatinib

Pemigatinib, a selective oral inhibitor of FGFR types 1, 2, and 3, has been approved by the FDA and EMA to treat adult patients with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma with a fusion or other rearrangement of the FGFR2 gene. The approval is based on the results of one phase 2 clinical trial in this patient population.[96] The NCCN recommends pemigatinib as a subsequent line treatment which is useful in some circumstances for unresectable or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements following disease progression.[34] [48] NICE recommends pemigatinib as an option for relapsed or refractory advance cholangiocarcinoma with FGFR2 fusion or rearrangement that has progressed after systemic therapy.[97]

Zanidatamab

Zanidatamab, a bispecific antibody that simultaneously binds two nonoverlapping epitopes of HER2, has received breakthrough therapy designation from the FDA for patients with previously treated HER2 gene-amplified biliary tract cancer. Zanidatamab has demonstrated meaningful clinical benefit with a manageable safety profile in patients with treatment-refractory, HER2-positive biliary tract cancer in one phase 2B single-arm clinical trial (HERIZON-BTC-01).[98]

Silmitasertib

Silmitasertib, a small molecule casein kinase 2 (CK2) inhibitor, has received orphan drug designation by the FDA for biliary tract cancers. One phase 1B/2 study showed preliminary evidence for the efficacy of silmitasertib when combined with gemcitabine and cisplatin in patients with locally advanced or metastatic cholangiocarcinoma, and a phase 3 trial is planned.[99]

ZB131

ZB131 is a monoclonal antibody with a high affinity and specificity for cancer-specific plectin (a cell surface protein associated with many aggressive cancers). The FDA has granted ZB131 orphan drug status for the treatment of cholangiocarcinoma. Interim data from one phase 1/2 trial showed that ZB131 had good tolerability with encouraging signs of activity and target engagement in heavily pretreated patients.[100] Further trials are warranted.

Monitoring

Monitoring

After treatment, imaging every 3 to 6 months is recommended for 2 years, then every 6 to 12 months for up to 5 years, and thereafter as clinically indicated.[34] [48] Liver function testing may be performed periodically to exclude recurring obstruction.

Complications

Complications	Timeframe	Likelihood
adverse effects of immune checkpoint inhibitor therapy	**short term**	**high**
The most common adverse effects of PD-1 or PD-L1 inhibitor therapies (e.g., durvalumab) are: anemia (45.4%), fatigue (34.3%), dysphagia (30.0%), neutropenia (19.6%), lymphopenia (10.2%), hypertension (9.3%), and elevated lipase (7.2%).[103] Other potential adverse effects include colitis, myocarditis, pericarditis, and skin toxicities. Guidelines for monitoring of patients and management of complications are available.[104]		
cholangitis	**short term**	**low**
More common in previously instrumented or obstructed biliary systems; treated with antibiotics and biliary drainage.		
biliary leak (surgical complication)	**short term**	**low**
Biliary leaks can occur in approximately 5% to 10% of complex bile duct anastomoses.		
biliary obstruction	**variable**	**medium**
Tumor overgrowth obstructing the biliary tree and requiring repeat resection, surgical bypass, or biliary stenting (percutaneous).		

Prognosis

Node-positive cholangiocarcinoma is a poor prognostic indicator of survival. Metastatic disease precludes resection and has a poor prognosis. The common early pattern of spread is to regional lymph nodes and to distant sites in the liver.

The 5-year survival for surgical resection alone ranges from 20% to 43%.[50] [51] [52] [53] For surgical resection with chemotherapy, the 5-year survival rate is 26%. The response rate to chemotherapy alone is <15%.[101] For liver transplant, there is a recurrence rate of 51% within 2 years of the procedure.[102]

Diagnostic guidelines

International

NCCN clinical practice guidelines in oncology: hepatobiliary cancers (https://www.nccn.org/guidelines/category_1) [48]

Published by: National Comprehensive Cancer Network **Last published:** 2023

NCCN clinical practice guidelines in oncology: biliary tract cancers (https://www.nccn.org/guidelines/category_1) [34]

Published by: National Comprehensive Cancer Network **Last published:** 2024

AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma (https://www.aasld.org/practice-guidelines) [7]

Published by: American Association for the Study of Liver Diseases **Last published:** 2022

Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma (http://www.journal-of-hepatology.eu/article/S0168-8278%2814%2900067-1/fulltext) [2]

Published by: International Liver Cancer Association **Last published:** 2014

Biliary tract cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (http://www.esmo.org/Guidelines) [49]

Published by: The European Society for Medical Oncology **Last published:** 2022

Guidelines for the diagnosis and management of cholangiocarcinoma (https://www.bsg.org.uk/resource-type/guidelines) [32]

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Treatment guidelines

International

AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma (https://www.aasld.org/practice-guidelines) [7]

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Adjuvant therapy for resected biliary tract cancer: ASCO clinical practice guideline (https://www.asco.org/research-guidelines/quality-guidelines/guidelines) [55]

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NCCN clinical practice guidelines in oncology: hepatobiliary cancers (https://www.nccn.org/guidelines/category_1) [48]

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NCCN clinical practice guidelines in oncology: biliary tract cancers (https://www.nccn.org/guidelines/category_1) [34]

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Images

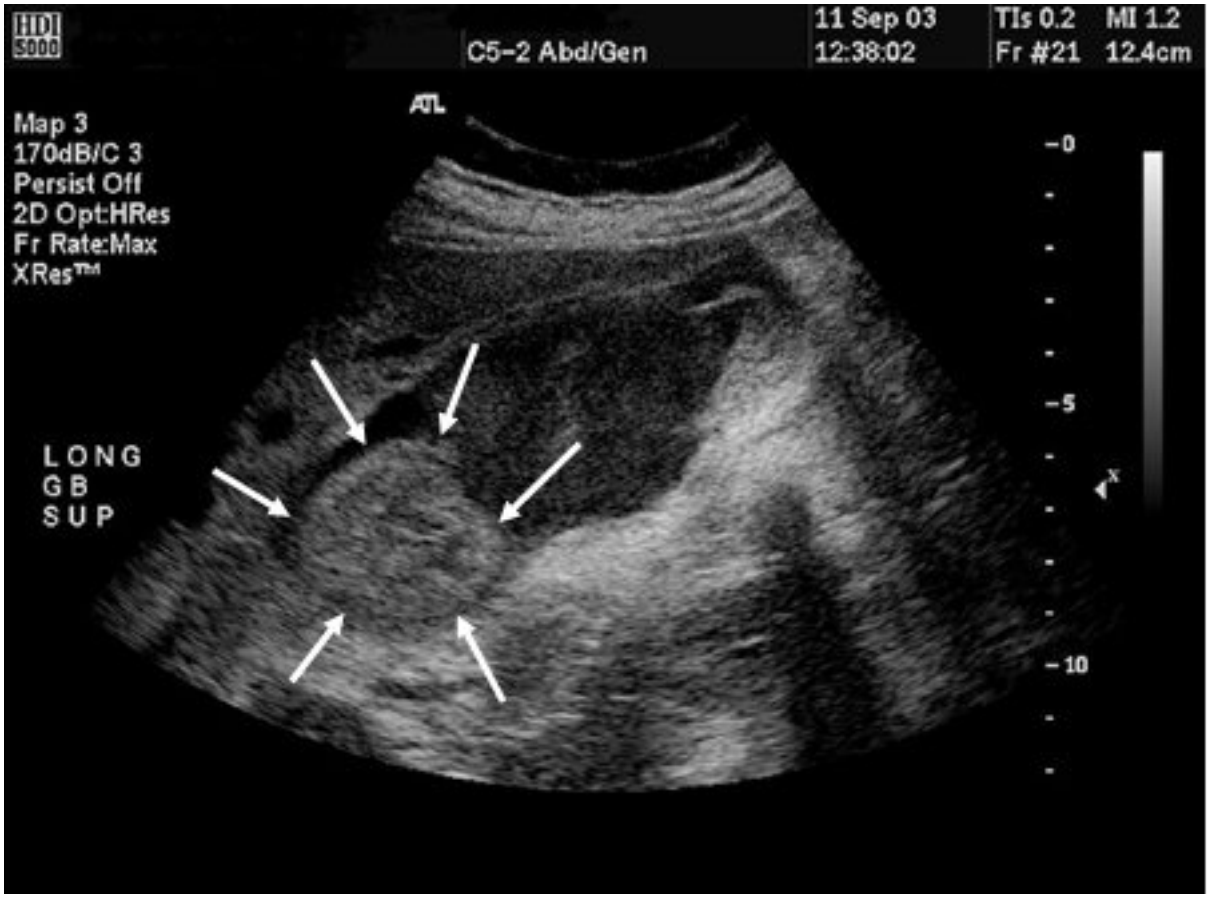

Figure 1: Gallbladder ultrasound of mass (arrows)

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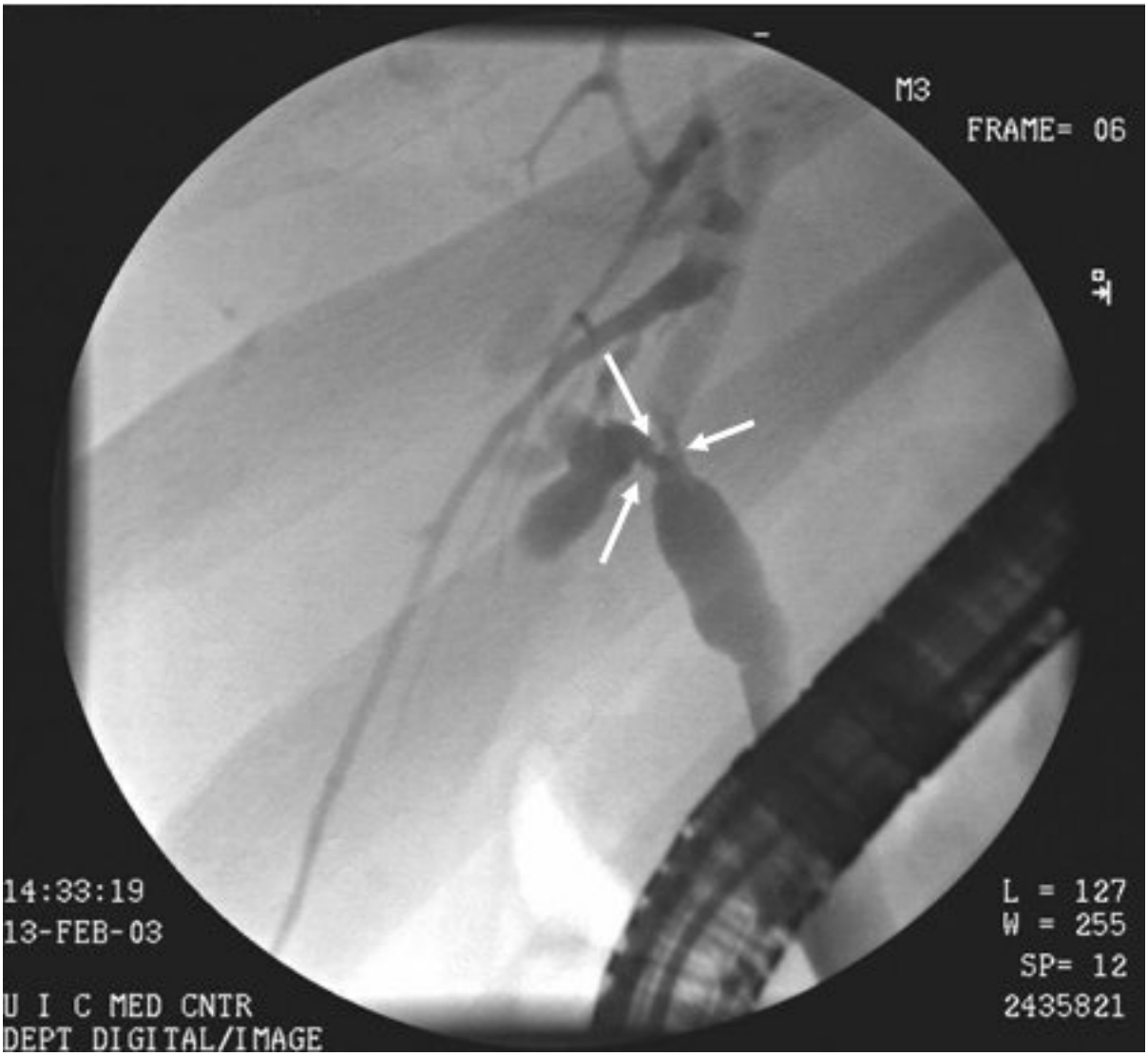

Figure 2: ERCP image of hilar cholangiocarcinoma: Klatskin tumor with stricture of duct bifurcation (arrows)

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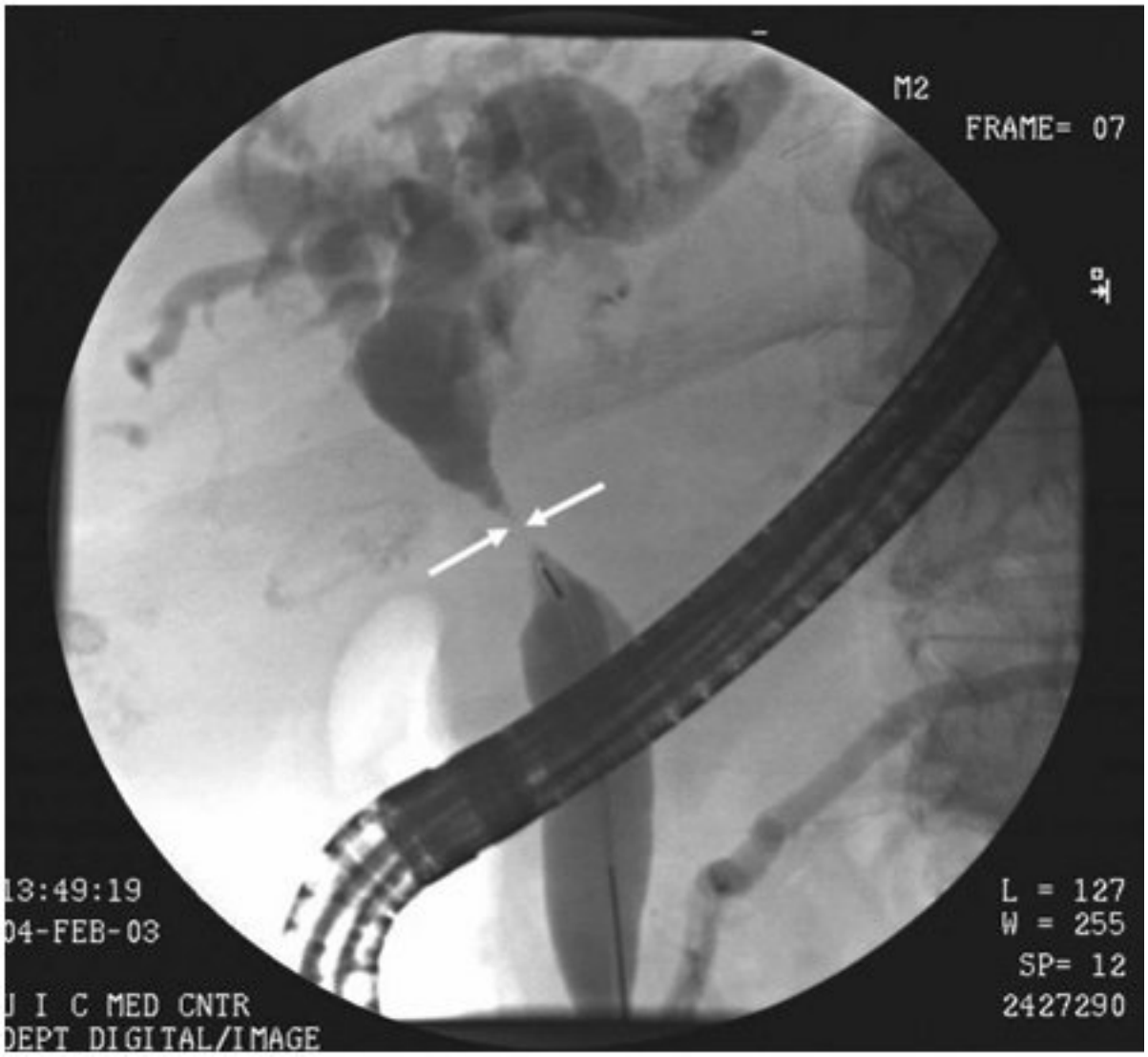

Figure 3: ERCP image of hepatic duct cholangiocarcinoma with duct stricture (arrows)

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Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

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numerals < 1: 0.25

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