Clinical manifestations and diagnosis of cholangiocarcinoma

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INTRODUCTION

Cholangiocarcinomas (bile duct cancers) arise from the epithelial cells of the bile ducts. Although they are rare in the United States, these cancers are highly lethal because most are locally advanced at presentation. (See "Epidemiology, pathogenesis, and classification of cholangiocarcinoma".)

The clinical manifestations and diagnosis of cholangiocarcinoma will be reviewed here. The epidemiology, pathogenesis, classification, and treatment of cholangiocarcinoma are discussed separately. Cancers of the gallbladder and ampulla of Vater are discussed as separate disease processes, although these structures are part of the biliary drainage system. (See "Epidemiology, pathogenesis, and classification of cholangiocarcinoma" and "Treatment of localized cholangiocarcinoma: Adjuvant and neoadjuvant therapy and prognosis" and "Treatment options for locally advanced, unresectable, but nonmetastatic cholangiocarcinoma" and "Gallbladder cancer: Epidemiology, risk factors, clinical features, and diagnosis" and "Ampullary carcinoma: Epidemiology, clinical manifestations, diagnosis and staging".)

TERMINOLOGY

Extrahepatic biliary tract malignancies were traditionally divided into cancers of the gallbladder, the extrahepatic ducts, and the ampulla of Vater, whereas intrahepatic tumors were classified as

primary liver cancers. More recently, the term cholangiocarcinoma has been used to designate bile duct cancers arising in the intrahepatic, perihilar, or distal (extrahepatic) biliary tree, exclusive of gallbladder and ampulla of Vater (figure 1) [1-3].

Approximately 5 to 10 percent of cholangiocarcinomas are intrahepatic. Intrahepatic cholangiocarcinomas can originate from either small intrahepatic ductules (peripheral cholangiocarcinomas) or large intrahepatic ducts proximal to the bifurcation of the right and left hepatic ducts. The extrahepatic bile ducts are divided into perihilar (including the confluence itself) and distal segments, with the transition occurring proximal to the cystic duct (figure 1) [2]. Cancers arising in the perihilar region, which account for 60 to 70 percent of extrahepatic cholangiocarcinomas, have been further classified according to the pattern of involvement of the hepatic ducts (the Bismuth-Corlette classification) (figure 2) [4,5]. Tumors involving the hepatic duct bifurcation (hilar cholangiocarcinomas) are collectively referred to as Klatskin tumors.

Type IV tumors, defined as tumor invasion of the second order biliary radicles bilaterally, are associated with a higher rate of positive surgical margins and significantly poorer overall survival after resection compared with types I to III [6]. The most recent (2017) revision of the tumor, node, metastasis (TNM) classification no longer considers type IV tumors to represent a T4 primary tumor. (See 'Tumor staging' below.)

CLINICAL PRESENTATION

Signs and symptoms — Extrahepatic cholangiocarcinomas usually become symptomatic when the tumor obstructs the biliary drainage system. Symptoms related to biliary obstruction include jaundice, pruritus, clay-colored stools, and dark urine. Other common symptoms include abdominal pain (30 to 50 percent), weight loss (30 to 50 percent), and fever (up to 20 percent) [7-9]. The pain is generally described as a constant dull ache in the right upper quadrant. Malaise, fatigue, and night sweats may be present [9]. Cholangitis is an unusual presentation.

Cholangiocarcinomas involving only the intrahepatic ducts (approximately 20 percent of all cholangiocarcinomas [10]) may present differently. Affected patients are less likely to be jaundiced. Instead, they usually have a history of dull right upper quadrant pain, weight loss, and an elevated alkaline phosphatase. Some patients are asymptomatic, with the lesions detected incidentally when imaging is obtained as part of the workup of abnormal liver blood tests [11], or during screening for hepatocellular carcinoma (HCC) in patients with hepatitis C

viral (HCV) infection and cirrhosis or in those with chronic hepatitis B virus infection. (See 'Laboratory abnormalities' below.)

Patients with primary sclerosing cholangitis (PSC) are at an elevated risk for cholangiocarcinoma, especially perihilar disease. The development of cholangiocarcinoma in such patients is often heralded by rapid clinical deterioration with a declining performance status, jaundice, weight loss, and abdominal discomfort. (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis", section on 'Cholangiocarcinoma'.)

Physical examination — On examination, patients with extrahepatic cholangiocarcinoma may have jaundice (90 percent), hepatomegaly (25 to 40 percent), a right upper quadrant mass (10 percent), or fever (2 to 14 percent) [7]. A palpable gallbladder occurs rarely. A palpable gallbladder in a jaundiced patient (Courvoisier sign or Courvoisier law) was previously thought to be a sign of malignancy (pancreatic or biliary) rather than other causes of biliary obstruction [12]. However, there are exceptions to this rule (eg, chronic pancreatitis, parasitic biliary obstruction, congenital choledochal cyst, common hepatic duct obstruction proximal to the takeoff of the cystic duct [12]), and the diagnostic utility of this physical examination finding is limited. (See "Choledocholithiasis: Clinical manifestations, diagnosis, and management", section on 'Physical examination'.)

Findings in patients with intrahepatic cholangiocarcinoma may include right upper quadrant tenderness, signs of weight loss, or rarely fever [7].

Rarely, patients with cholangiocarcinoma may also have cutaneous findings associated with paraneoplastic syndromes such as Sweet syndrome (picture 1) [13], porphyria cutanea tarda (picture 2) [14], acanthosis nigricans (picture 3) [15,16], and erythema multiforme (picture 4) [17]. (See "Sweet syndrome (acute febrile neutrophilic dermatosis): Pathogenesis, clinical manifestations, and diagnosis", section on 'Clinical manifestations' and "Acanthosis nigricans", section on 'Malignancy-associated acanthosis nigricans' and "Erythema multiforme: Pathogenesis, clinical features, and diagnosis", section on 'Cutaneous' and "Porphyria cutanea tarda and hepatoerythropoietic porphyria: Pathogenesis, clinical manifestations, and diagnosis", section on 'Blistering skin lesions and other cutaneous manifestations'.)

Laboratory abnormalities — All patients presenting with jaundice or right upper quadrant pain should have an assay of serum aminotransferases, alkaline phosphatase, and bilirubin (total, direct, and indirect) to determine if cholestasis is present. (See "Diagnostic approach to the adult with jaundice or asymptomatic hyperbilirubinemia", section on 'Initial laboratory tests and interpretation' and "Evaluation of the adult with abdominal pain", section on 'Epigastric pain'.)

For patients with extrahepatic cholangiocarcinomas, liver biochemical tests typically suggest biliary obstruction, with elevations in total bilirubin (often above 10 mg/dL [171 micromol/L]), direct bilirubin, and alkaline phosphatase (usually increased 2- to 10-fold).

Transaminase levels (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) may initially be normal. However, chronic biliary obstruction often leads to liver dysfunction and a pattern consistent with hepatocellular injury, with elevated transaminases and a prolonged prothrombin time/elevated international normalized ratio (INR).

Patients with an intrahepatic cholangiocarcinoma usually have abnormal levels of alkaline phosphatase, whereas serum bilirubin levels are usually normal or only slightly elevated [7]. Elevated levels of 5'-nucleotidase and gamma-glutamyl transpeptidase confirm the hepatobiliary origin of the excess alkaline phosphatase. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Confirming an elevated alkaline phosphatase is of hepatic origin'.)

Patients with primary sclerosing cholangitis who are undergoing screening for cholangiocarcinoma may present only with an abnormally elevated serum level of the tumor marker carbohydrate antigen 19-9 (CA 19-9). (See 'CA 19-9' below.)

Some patients with cholangiocarcinoma may also have findings associated with hypercalcemia of malignancy (hypercalcemia, hypophosphatemia, low parathyroid hormone levels, and low vitamin D levels) [18]. (See "Hypercalcemia of malignancy: Mechanisms".)

Radiographic findings — Most jaundiced patients undergo transabdominal ultrasonography to confirm biliary ductal dilatation, localize the site of the obstruction, and exclude gallstones [19]. In cases where ultrasound can't confirm a benign cause of biliary obstruction as the cause of jaundice, axial (cross-sectional) imaging (computed tomography [CT] scanning or magnetic resonance imaging [MRI]) should be performed. (See 'Imaging studies' below.)

Extrahepatic bile duct cancers may not be directly visualized, especially if small, but indirect signs (ductal dilatation) may point toward the diagnosis. An obstructing malignant lesion is suggested by ductal dilatation (>6 mm in normal adults) in the absence of stones. Proximal extrahepatic lesions may cause dilation of the intrahepatic ducts alone, while both intrahepatic and extrahepatic ducts are dilated with more distal lesions [19]. (See 'Ultrasound' below.)

Intrahepatic cholangiocarcinoma tumor growth patterns include the mass-forming type, the periductal-infiltrating type with associated intrahepatic ductal dilation, and a mixed type. The purely mass-forming type is most common, accounting for approximately 60 percent of all intrahepatic cholangiocarcinomas, whereas the purely periductal and mixed types account for

approximately 20 percent of cases each [3]. Mass lesions on imaging studies can be detected incidentally in cirrhotic patients undergoing HCC screening. Focal segmental bile duct dilation distal to an intrahepatic mass can be a highly suggestive feature of cholangiocarcinoma.

Mixed hepatocellular-cholangiocellular carcinoma, also referred to as primary liver carcinoma with biphenotypic differentiation, is a distinct subtype of cholangiocarcinoma that has a distinct appearance on cross sectional imaging [20]. A strong enhancing rim and an irregular shape on gadoxetic acid-enhanced MRI favor a mixed tumor, while a lobulated shape, weak rim, and a target appearance favor a mass-forming intrahepatic cholangiocarcinoma. These mixed tumors are staged as intrahepatic cholangiocarcinomas and not hepatocellular cancers. (See 'MRI and MRCP' below and 'Tumor staging' below.)

Metastatic disease — Uncommonly, patients present because of signs or symptoms related to metastatic disease or evidence of metastatic disease on imaging:

- Intrahepatic cholangiocarcinomas most commonly metastasize to other intrahepatic locations, to the peritoneum, and subsequently to lungs and pleura.
- For perihilar cholangiocarcinomas, the liver is a common site of metastases, but spread to extra-abdominal sites (eg, peritoneum, lung, brain, and bone) is uncommon.
- For distal cholangiocarcinomas, distant metastases occur late in the course of the disease and are most often found in the liver, lungs, and peritoneum.

APPROACH TO THE PATIENT

When to consider cholangiocarcinoma — In patients who do not have primary sclerosing cholangitis (PSC), a diagnosis of cholangiocarcinoma should be considered if there are signs of biliary obstruction (eg, jaundice, abnormal liver tests in a cholestatic pattern, bile duct dilation on imaging studies) without an alternative explanation (eg, choledocholithiasis or a pancreatic head lesion). The diagnosis should also be considered in patients found to have an isolated intrahepatic mass on imaging and a normal serum level of alpha-fetoprotein (AFP). (See 'Clinical presentation' above and 'Differential diagnosis' below and 'Alpha-fetoprotein' below.)

In patients with PSC, cholangiocarcinoma should be considered if there is rapid clinical deterioration with jaundice, weight loss, and abdominal pain. The presence of progressive biliary dilatation in the setting of a dominant stricture or thickening of the bile duct wall should also raise a strong suspicion of cholangiocarcinoma. Cholangiocarcinoma should also be considered if screening tests (ie, carbohydrate antigen [CA] 19-9 and/or magnetic resonance

cholangiopancreatography [MRCP]) are abnormal. (See 'CA 19-9' below and 'MRI and MRCP' below and "Primary sclerosing cholangitis in adults: Management", section on 'Gallbladder carcinoma and cholangiocarcinoma'.)

Diagnostic approach — The diagnostic approach varies depending on where the suspected lesion is (distal extrahepatic, perihilar, or intrahepatic (figure 1)) and if the patient has a history of PSC (algorithm 1 and algorithm 2). All patients suspected of a cholangiocarcinoma should have tumor markers (CA 19-9, carcinoembryonic antigen [CEA], and for patients with intrahepatic lesions, AFP) checked. With the caveat that biliary ductal obstruction alone can cause an elevation in CA 19-9, elevated tumor markers may support a diagnosis of cholangiocarcinoma, or in the case of an elevated AFP, suggest an alternative diagnosis (hepatocellular carcinoma [HCC]). If elevated, tumor markers may also be helpful in monitoring patients for recurrence after therapy. The role of assaying for serum IgG4 is unclear. A serum concentration of IgG4 can be obtained if IgG4-related sclerosing cholangitis is in the differential diagnosis (eg, in a patient with autoimmune pancreatitis). (See 'Tumor markers' below and "Pathogenesis and clinical manifestations of IgG4-related disease", section on 'Clinical manifestations'.)

The location of the lesion is suggested by the patient's clinical presentation and the initial radiographic findings. Often, a patient will have undergone transabdominal ultrasound as part of the evaluation for jaundice. If a patient is suspected of having cholangiocarcinoma but has not undergone imaging (eg, in a patient who is found to have an elevated CA 19-9), the initial imaging test is typically a contrast-enhanced MRI scan/MRCP or a multiphasic contrast-enhanced multidetector-row computed tomography (MDCT) scan. (See 'Clinical presentation' above.)

In some patients, the first test obtained may be an endoscopic retrograde cholangiopancreatography (ERCP). This most often occurs in a patient in whom there is a high suspicion for choledocholithiasis. (See "Overview of endoscopic retrograde cholangiopancreatography (ERCP) in adults", section on 'Patient selection'.)

Imaging test findings that may help localize the lesion include:

- Distal extrahepatic cholangiocarcinoma – Intrahepatic and extrahepatic biliary ductal dilation [19]. An abrupt change in ductal diameter may be seen.
- Perihilar cholangiocarcinoma – Intrahepatic ductal dilatation with normal-caliber extrahepatic ducts.

- Intrahepatic cholangiocarcinoma – Mass lesion, often in a noncirrhotic liver, that lacks radiographic characteristics of a primary HCC. (See "Clinical features and diagnosis of hepatocellular carcinoma", section on 'Imaging diagnosis of HCC' and "Clinical features and diagnosis of hepatocellular carcinoma", section on 'Non-high-risk patients'.)

While cholangiocarcinoma is often suspected based on ultrasound findings, additional imaging studies (eg, MRI/MRCP, ERCP, endoscopic ultrasound [EUS]) are essential for assisting with diagnosis and for planning management. The diagnostic imaging evaluation is designed to eliminate benign tumors or gallstones from the differential diagnosis, to establish the location and extent of tumor invasion, and to determine if metastases have developed. The specific imaging tests obtained will depend upon the location of the tumor and if the patient has PSC. (See 'Patients with primary sclerosing cholangitis' below.)

Suspected distal extrahepatic cholangiocarcinoma — In the patient with evidence of distal extrahepatic obstruction, EUS or ERCP is preferred as the next step in the evaluation, as the studies permit direct visualization of the area of abnormality, enable a biopsy (either fine-needle aspiration [FNA] or brush cytology), and in the case of ERCP, allow for the possibility of therapeutic intervention (eg, stent placement). We generally start with an EUS unless the patient requires endoscopic drainage or the lesion is not amenable to EUS-guided FNA because of its location.

We prefer EUS because ERCP involves injecting contrast into the bile duct, putting patients at risk for ascending cholangitis if there is impaired biliary drainage. However, patients undergoing FNA may be at risk of seeding the biopsy tract with malignant cells. If ERCP is performed, brush cytology should be obtained from any lesions or dominant strictures (see "Endoscopic ultrasound-guided fine needle aspiration in the gastrointestinal tract", section on 'Adverse events'). Intraductal ultrasound (IDUS), if available, can also be considered to help differentiate benign from malignant strictures. While not widely available, cholangioscopy can be performed to directly visualize the bile ducts and to biopsy indeterminant strictures. (See "Cholangioscopy and pancreatoscopy" and "Infectious adverse events related to endoscopic retrograde cholangiopancreatography (ERCP)", section on 'Acute cholangitis'.)

If the endoscopic images and/or tissue samples are highly suggestive of cholangiocarcinoma, we proceed with tumor staging. However, if endoscopic imaging and tissue sampling are nondiagnostic, we obtain an MRI or multiphasic contrast-enhanced MDCT scan, if not yet obtained. If a mass is visible on cross-sectional imaging, we proceed with CT- or MRI-guided biopsy (though as with EUS-guided FNA there is a risk of seeding the biopsy tract with tumor cells). If that fails or a mass is not visible on cross-sectional imaging, surgery may be required to confirm the diagnosis (see 'Need for tissue diagnosis' below and 'Tumor staging' below). If

radiographic findings are sufficiently suspicious for cholangiocarcinoma such that a negative biopsy would be characterized as a potential false-negative and the tumor appears resectable, then biopsy is not indicated.

Suspected perihilar cholangiocarcinoma — For hilar lesions, MRCP is emerging as the imaging technique of choice [21], while the use of invasive cholangiography (ERCP or percutaneous cholangiography) is diminishing. Patients with hilar tumors are at risk for ascending cholangitis following ERCP, since achieving complete biliary drainage can be difficult. Multiphasic contrast-enhanced MDCT scan is an alternative in patients who cannot undergo MRI, but it has limited sensitivity for extraregional nodal disease (ie, metastases to the periaortic, pericaval, or celiac artery lymph nodes, and peritoneum). (See 'Imaging studies' below.)

If the imaging studies and/or tissue samples are highly suggestive of cholangiocarcinoma, we proceed directly with tumor staging. However, if the diagnosis remains in doubt, we proceed with ERCP with brush cytology (with or without IDUS). Where available, cholangioscopy can be performed to evaluate the bile ducts. Alternatively, MRI- or CT-guided biopsy can be obtained if a mass lesion is seen on imaging, though there is a small risk of seeding the biopsy tract with malignant cells. If the diagnosis remains in doubt, surgery may be required to confirm the diagnosis. (See 'Need for tissue diagnosis' below and 'Tumor staging' below and "Cholangioscopy and pancreatoscopy".)

Suspected intrahepatic cholangiocarcinoma — When an intrahepatic lesion is suspected, the next step is cross-sectional imaging (multiphasic contrast-enhanced MDCT scan or MRI) to differentiate between cholangiocarcinoma and HCC, provided the patient is not known to have or suspected of having an extrahepatic malignancy, in which case metastatic disease should be ruled out first. If the initial imaging test is nondiagnostic, the other imaging modality (MDCT or MRI) can then be obtained. Resection or biopsy of the lesion may be required if the diagnosis remains uncertain. (See 'Intrahepatic cholangiocarcinoma' below.)

The approach to the evaluation of patients with a solid liver lesion is discussed in detail separately. (See "Approach to the adult patient with an incidental solid liver lesion" and "Approach to the adult patient with an incidental solid liver lesion", section on 'Diagnostic approach'.)

Patients with primary sclerosing cholangitis — Radiographic diagnosis of a cholangiocarcinoma can be challenging, particularly in patients with PSC. In such cases, patients may have a dominant benign biliary stricture that may be difficult to differentiate from cholangiocarcinoma. Mass lesions are infrequently identified on imaging, and patients often do

not develop significant intrahepatic biliary ductal dilation. Worrisome imaging findings include progression of stricture on serial cholangiograms, marked biliary dilation above a dominant stricture, and a polypoid ductal mass ≥1 cm in diameter.

We start the evaluation with MRCP to document the segmental extent of ductal involvement, search for intrahepatic metastases, and identify aberrant ductal anatomy (algorithm 2). If the MRCP is nondiagnostic or if a dominant stricture is identified, we will obtain an ERCP with brush cytology with or without IDUS. Where available, cholangioscopy can be performed to evaluate the bile ducts and obtain biopsies. Typically the biopsies are directed at dominant strictures or abnormal appearing tissue. (See 'Need for tissue diagnosis' below and 'Tumor staging' below and 'PET scan' below and 'MRI and MRCP' below and 'Endoscopy and percutaneous cholangiography' below and "Cholangioscopy and pancreatoscopy".)

If the MRCP, ERCP, and/or tissue samples are highly suggestive of cholangiocarcinoma, we proceed directly with tumor staging. However, if the diagnosis remains in doubt, a positron emission tomography (PET) scan may be helpful. If the PET scan is nondiagnostic, we repeat imaging with MRCP in three months. If that study is again nondiagnostic, we then follow the patient closely clinically.

Need for tissue diagnosis — A tissue diagnosis can be obtained by a variety of means in patients suspected of having cholangiocarcinoma (brush cytology, FNA, CT/MRI-guided biopsy), but obtaining tissue may be difficult in patients with perihilar lesions. The necessity of establishing a tissue diagnosis prior to surgery depends upon the clinical situation. It is not critical for planning surgery in potentially operable patients with characteristic findings of malignant biliary obstruction or a solitary intrahepatic mass and may not be necessary for planning palliative therapy, such as biliary drainage, in unresectable cases. In addition, FNA or CT/MRI-guided biopsy can rarely result in seeding of the biopsy tract with malignant cells, which may preclude an otherwise eligible transplantation candidate from undergoing transplantation. Thus, we recommend that in patients with perihilar tumors, the case be discussed with the transplantation team prior to proceeding with tissue sampling.

Tissue diagnosis is most important in the following circumstances [22]:

- Strictures of clinically indeterminate origin (eg, in patients with a history of biliary tract surgery, bile duct stones, or PSC)
- A situation where the physician or patient would be reluctant to proceed with surgery without a tissue diagnosis, or if the patient or family's acceptance and adjustment to the diagnosis would be facilitated by having a definitive diagnosis

- To provide documentation of the diagnosis for patients being treated nonoperatively (eg, chemotherapy and/or radiation therapy only)

Tumor staging — The most recent version (eighth edition) of the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging criteria for distal, perihilar, and intrahepatic cholangiocarcinomas contains a number of changes in the tumor (T) and node (N) stage definitions and the AJCC prognostic stage groupings compared with earlier editions (table 1 and table 2 and table 3) [1-3]. These changes have led to better prognostic stratification for all three sites. (See "Epidemiology, pathogenesis, and classification of cholangiocarcinoma", section on 'TNM staging classifications'.)

Preoperative staging starts with radiographic and endoscopic studies, some of which may have already been done as part of the diagnostic evaluation (in which case the studies do not need to be repeated).

Patterns of spread — The purpose of the staging evaluation is to assess local invasion and resectability, and to detect nodal and distant disease spread [23]:

- The lymph node drainage patterns for intrahepatic cholangiocarcinomas demonstrate laterality. Left-sided intrahepatic cholangiocarcinomas mainly spread to the nodes along the lesser curvature of the stomach and to inferior phrenic lymph nodes [3]. By contrast, intrahepatic cholangiocarcinomas of the right liver have a lymphatic drainage pattern similar to that of the gallbladder, and preferentially drain to the right-sided hilar lymph nodes and, subsequently, to portocaval nodes. Regional lymph nodes for left-sided lesions include inferior phrenic, hilar (common bile duct, hepatic artery, portal vein, and cystic duct), and gastrohepatic lymph nodes [3]. For right-sided tumors, the regional nodes include the hilar, periduodenal, and peripancreatic lymph nodes. For all intrahepatic cholangiocarcinomas, spread to the celiac, periaortic, and/or pericaval lymph nodes is considered distant metastatic disease. The usual metastatic pattern is to intrahepatic sites (which is classified in the tumor [T] stage category as multiple tumors), to the peritoneum, and subsequently, to the bone, lungs, and pleura.

- Perihilar cholangiocarcinomas are characterized by intrahepatic ductal extension, as well as spread along perineural and periductal lymphatic channels. Hilar and pericholedochal nodes in the hepatoduodenal ligament are most often involved. Hilar, cystic duct, choledochal, portal, hepatic arterial, and posterior pancreaticoduodenal lymph nodes are classified as regional nodes [2]. Lymph node metastases distal to the hepatoduodenal ligament are classified as distant metastases.

The liver is a common site of metastases, and spread to extra-abdominal sites (eg, peritoneum, lung, brain, and bone) is uncommon. In addition to these spreading routes, the left peripheral type or hilar type of cholangiocarcinoma tends to spread along the left gastric nodes through the lesser curvature.

- The regional nodes for distal cholangiocarcinomas are the same as for exocrine cancers of the pancreatic head (along the common bile duct, common hepatic artery, portal vein, posterior and anterior pancreaticoduodenal nodes, and nodes along the right lateral wall of the superior mesenteric artery) [1]. Distal cholangiocarcinomas can spread locally to involve the pancreas, duodenum, stomach, colon, or omentum. Distant metastases occur late in the course of the disease and are most often found in the liver, lungs, and peritoneum.

The staging workup — In general, we start the staging evaluation with MDCT scanning of the abdomen and pelvis, with or without MRCP. If there is no evidence of distant metastatic disease, extraregional lymph node involvement, or invasion of critical adjacent structures, we obtain a PET scan to look for occult metastases. If the PET scan is normal and the patient is a good surgical candidate, we proceed with laparoscopy. (See 'PET scan' below and 'Staging laparoscopy' below.)

Radiographic studies — The approach to tumor staging is somewhat center dependent, with many centers using a combination of MRCP and MDCT scan for initial staging. However, MRCP requires dedicated radiology personnel and a high level of technical expertise. If possible, MRCP should be performed before biliary drainage, since evaluation for biliary pathology is more difficult if the biliary tree is collapsed.

If metastatic disease is not seen with cross-sectional imaging and the patient is an operative candidate, we suggest integrated PET/CT to rule out occult metastases. Modern CT and MRI techniques almost always appropriately characterize portal vein or hepatic arterial involvement. However, if cross-sectional imaging is equivocal, duplex ultrasound (color Doppler) can be used to evaluate vascular involvement (ie, compression, encasement, or thrombosis of the portal vein; encasement or occlusion of the hepatic artery). Invasion into the portal vein or hepatic artery is an important finding, as in some cases it may be an indicator of unresectability. (See 'MDCT' below and 'MRI and MRCP' below and 'PET scan' below and 'Ultrasound' below.)

Endoscopic studies — Cholangiography (ERCP or percutaneous transhepatic cholangiography [PTC]) may help with staging distal lesions or if preoperative drainage of the biliary tree is needed. PTC is generally preferred for imaging the proximal biliary system if there is complete obstruction of the distal biliary tree. (See 'Cholangiography' below.)

For distal bile duct lesions, EUS can visualize the local extent of the primary tumor and the status of regional lymph nodes. The sensitivity of EUS for imaging and staging proximal bile duct lesions is less than for distal lesions, and clinical experience is limited. (See 'Endoscopic ultrasound' below.)

IDUS can improve the accuracy of local tumor staging of bile duct carcinomas. IDUS detects early lesions, determines the longitudinal tumor extent, and identifies tumor extension into adjacent organs and major blood vessels with a diagnostic accuracy of nearly 100 percent. In particular, IDUS can accurately identify tumor invasion into the pancreatic parenchyma, portal vein, and right hepatic artery. (See 'Intraductal ultrasound' below.)

Staging laparoscopy — Despite the enhanced diagnostic capability of radiologic studies such as MRCP and MDCT, unless there is clear evidence of metastatic disease, resectability can ultimately only be determined by operative evaluation. Laparoscopy can identify the majority of patients with unresectable hilar and distal cholangiocarcinoma, thereby reducing the number of unnecessary laparotomies [24,25]. However, true resectability often can only be determined after a complete abdominal exploration [26].

DIFFERENTIAL DIAGNOSIS

The signs and symptoms associated with bile duct cancer are nonspecific, so the differential diagnosis is broad.

Jaundice with or without weight loss and abdominal pain — Patients with biliary obstruction due to cholangiocarcinoma usually present with conjugated hyperbilirubinemia (table 4), and the differential diagnosis includes choledocholithiasis, biliary obstruction from other malignant tumors (especially pancreatic cancer) or adenomas, intrahepatic cholestasis (eg, primary biliary cirrhosis, primary sclerosing cholangitis), and acute or chronic hepatocellular injury. (See "Classification and causes of jaundice or asymptomatic hyperbilirubinemia".)

The classic triad of symptoms that leads to suspicion for a primary pancreatobiliary malignancy (including cholangiocarcinoma) is painless jaundice, right upper quadrant pain, and weight loss. However, this triad may also be seen with benign causes (choledocholithiasis, benign bile duct strictures, sclerosing cholangitis [primary or IgG4-related], compression of the common bile duct by chronic pancreatitis) and metastatic cancer. (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis" and "Pathogenesis and clinical manifestations of IgG4-related disease", section on 'IgG4-related sclerosing cholangitis'.)

For most patients, abdominal ultrasound is the first imaging test obtained because it is sensitive for detecting gallstones and is better than CT scanning for measuring the degree of biliary dilation. However, if there is high suspicion for choledocholithiasis, other imaging studies (endoscopic retrograde cholangiopancreatography [ERCP], magnetic resonance cholangiopancreatography [MRCP]) may be more appropriate as initial tests. (See "Diagnostic approach to the adult with jaundice or asymptomatic hyperbilirubinemia", section on 'Evaluation for intrahepatic cholestasis'.)

Making a definitive diagnosis is important, since up to one-third of patients with symptoms and a cholangiogram suggestive of a bile duct malignancy will have either benign fibrosing disease or another malignancy with metastases that obstruct the bile ducts [27,28]. Liver biochemical tests are of little use in differentiating among these conditions, since all can be associated with conjugated hyperbilirubinemia and an elevated alkaline phosphatase.

While imaging can often distinguish among these diagnoses, definitive diagnosis may require intraoperative evaluation and/or histologic examination of tissue. (See 'Imaging studies' below.)

Abdominal pain — Pain involving the liver or biliary tree is generally located in the right upper quadrant (RUQ), but it may radiate to the back or epigastrium. Because hepatic pain only develops when the liver capsule is "stretched," most pain in the RUQ is related to the biliary tree. There are several benign biliary tract syndromes that cause RUQ pain, including cholelithiasis/biliary colic, choledocholithiasis, acute cholecystitis, acute cholangitis, and biliary dyskinesia. In addition, viral or drug-induced hepatitis can sometimes cause acute RUQ pain. Other causes of RUQ pain that should be considered in the differential diagnosis include acute pancreatitis, dyspepsia, pneumonia, empyema, and a subdiaphragmatic abscess (table 5). (See "Causes of abdominal pain in adults", section on 'Upper abdominal pain syndromes'.)

Weight loss — Some of the causes of involuntary weight loss include malignancies, endocrinopathies, and psychiatric diseases. The approach to the patient with weight loss is discussed in detail elsewhere. (See "Approach to the patient with unintentional weight loss".)

Intrahepatic mass — Intrahepatic cholangiocarcinomas usually present as a malignant-appearing mass lesion in a noncirrhotic liver. There are numerous causes of solid liver lesions, both benign and malignant. The main differential is usually with a primary hepatocellular carcinoma or with metastatic adenocarcinoma. Tumor markers, liver biopsy with immunohistochemical staining, and radiographic imaging typically help with the distinction. (See "Approach to the adult patient with an incidental solid liver lesion" and 'Alpha-fetoprotein' below and 'Intrahepatic cholangiocarcinoma' below.)

Extrahepatic mass — Hilar cholangiocarcinoma can usually be differentiated from hilar adenopathy or benign stricture. Lymphadenopathy compresses and displaces rather than invades the bile ducts. Benign strictures, which typically develop after cholecystectomy or distal gastric surgery, are short and cause smooth, symmetric narrowing of the common bile duct. Rarely, lymphoma or sarcoidosis involving the bile ducts may be indistinguishable from cholangiocarcinoma [29,30].

Distal cholangiocarcinomas that arise from the point of intersection of the cystic duct to the ampulla of Vater (figure 1) can be difficult to distinguish from early pancreatic or ampullary cancer. Sometimes, these tumors are categorized as "periampullary neoplasms" and are only identified as distal cholangiocarcinomas after histologic examination of the resection specimen. (See "Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer", section on 'Pancreatic mass seen on an imaging study'.)

SPECIFIC TESTS

This section will review the characteristics of the tests used in the diagnosis of cholangiocarcinoma. The clinical manifestations (including general laboratory test findings) and general approach to the diagnosis of cholangiocarcinoma are discussed above. (See 'Clinical presentation' above and 'Approach to the patient' above.)

Serologic tests

Tumor markers — Although not specific for cholangiocarcinoma, the presence of certain tumor markers in the serum of patients with cholangiocarcinoma may be of diagnostic value. Most of the studies in this area have been geared toward identifying cholangiocarcinoma in patients with primary sclerosing cholangitis (PSC). Such patients have an increased incidence of cholangiocarcinoma, which is difficult to diagnose radiographically due to the underlying pathology. (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis", section on 'Cholangiocarcinoma'.)

Carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) are the two markers that have been best studied, although their diagnostic utility is limited due to significant overlap with benign disease and other malignancies, and low sensitivity for early stage cholangiocarcinoma. Alpha-fetoprotein (AFP) is used to help differentiate intrahepatic cholangiocarcinoma from hepatocellular carcinoma (HCC).

CA 19-9 — CA 19-9 is an established serum marker for the diagnosis of cholangiocarcinoma, although it is reported to have a wide variation in sensitivity (50 to 90

percent) and specificity (54 to 98 percent) [31-33]. Serum levels of CA 19-9 are widely used for detecting cholangiocarcinoma in patients with PSC [31,34-37]. Elevated levels of CA 19-9 prior to treatment are associated with a poorer prognosis [38,39], and CA 19-9 concentrations >1000 unit/mL are consistent with advanced disease, often involving the peritoneum [36,40,41]. If initially elevated, serum CA 19-9 levels may be useful for following the effect of treatment and to detect disease recurrence. (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis", section on 'Cholangiocarcinoma'.)

However, there are limitations to the use of serum CA 19-9 as a diagnostic tumor marker for cholangiocarcinoma:

- The specificity of CA 19-9 is limited. CA 19-9 is frequently elevated in patients with various benign pancreaticobiliary disorders, including cholangitis, and with other malignancies, including pancreatic cancer (table 6). (See "Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer", section on 'Role of tumor markers'.)

  The optimal cutoff value that best discriminates between benign or malignant biliary tract disease is influenced by the presence of cholangitis (suggested by the presence of fever, leukocytosis, and right upper quadrant pain) and/or cholestasis (defined as a serum bilirubin >3 mg/dL [51.3 micromol/L]). In one report, a CA 19-9 cutoff value of ≥37 unit/mL was 78 percent sensitive and 83 percent specific for malignant disease in patients who did not have cholangitis or cholestasis [31]. By contrast, if the patient had cholangitis or cholestasis, the sensitivity dropped to 74 percent and the specificity to 42 percent when a cutoff of ≥37 unit/mL was used. In patients with cholestasis or cholangitis, increasing the cutoff value to ≥300 unit/mL was optimal for increasing specificity (87 percent), but at the expense of reduced sensitivity (approximately 40 percent). (See "Glossary of common biostatistical and epidemiological terms".)

  Thus, in patients with symptoms of acute cholangitis, serum CA 19-9 concentrations should ideally be reevaluated after recovery.

- For patients with PSC, periodic assay of CA 19-9 is one method used for cholangiocarcinoma surveillance. (See "Primary sclerosing cholangitis in adults: Management", section on 'Gallbladder carcinoma and cholangiocarcinoma'.)

  However, the optimal cutoff value that provides the best balance between sensitivity and specificity in this setting is unclear, as evidenced by the following:

  - In a three-year prospective study of 75 patients with PSC without clinical signs of cholangiocarcinoma, elevated serum levels of CA 19-9 (≥37 unit/mL) were not useful for

diagnosing cholangiocarcinoma because of limited specificity [42].

- The use of higher cutoff values enhances specificity, albeit at the expense of sensitivity. In a report of 218 patients with PSC (14 of whom had cholangiocarcinoma), a serum CA 19-9 level of 129 unit/mL was 79 percent sensitive and 99 percent specific for the diagnosis of cholangiocarcinoma [35]. However, the positive predictive value (the likelihood that a patient with PSC and a CA 19-9 level of 129 unit/mL or more has cholangiocarcinoma) was only 57 percent.

  A low positive predictive value (63 percent) was reported in a second study that used the same cutoff value [40]. In some cases, the elevated CA 19-9 could be attributed to recurrent bacterial cholangitis, but in many cases it was unexplained.

We typically use a CA 19-9 value ≥129 unit/mL to increase suspicion for a cholangiocarcinoma in patients with PSC, especially in the presence of a dominant hilar stricture, though the current United Network for Organ Sharing policy for transplantation for cholangiocarcinoma uses a cutoff of ≥100 unit/mL [43].

- CA 19-9 requires the presence of the Lewis blood group antigen (a glycosyl transferase) to be expressed. Individuals with a Lewis-negative phenotype (an estimated 5 to 10 percent of the population) do not make CA 19-9 and therefore will not benefit from CA 19-9 testing. (See "Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer", section on 'Carbohydrate antigen 19-9'.)

CEA — Serum levels of CEA may be elevated in cholangiocarcinoma. One large series evaluated serum CEA levels in 333 patients with PSC, of whom 44 (13 percent) were diagnosed with cholangiocarcinoma either by histologic confirmation or at least one year of clinical follow-up [34]. A serum CEA level >5.2 ng/mL had a sensitivity and specificity of 68 and 82 percent, respectively.

By itself, serum CEA is neither sufficiently sensitive nor specific to diagnose cholangiocarcinoma. Many conditions other than cholangiocarcinoma can increase serum levels of CEA. In addition to a variety of gastrointestinal tract primary cancers and breast cancer, noncancer-related causes of an elevated CEA include gastritis, peptic ulcer disease, diverticulitis, liver disease, chronic obstructive pulmonary disease, diabetes, and any acute or chronic inflammatory state. (See "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Tumor markers'.)

However, if levels are elevated, they may be useful for following the effects of treatment and to detect disease recurrence, particularly if CA 19-9 levels are not initially elevated.

Combined CEA and CA 19-9 — The use of a combined index of serum CA 19-9 and CEA (CA 19-9 + [CEA x 40]) has been proposed to enhance the ability to diagnose cholangiocarcinoma in patients with PSC; however, the data are mixed:

- In one series, using a cutoff of 400 U, this index correctly identified 10 of 15 patients with cholangiocarcinoma, including 6 of 11 with radiographically occult disease; there were no false positives [37].

- In the series mentioned above with 333 patients with PSC, 45 patients (eight of whom had cholangiocarcinoma) had both tests [34]. Using the cutoff values of CEA >5.2 ng/mL and CA 19-9 >180 unit/mL, the sensitivity and specificity for the use of both tests were 100 percent and 78 percent, respectively.

- However, in another study of 72 patients with PSC, the use of CA 19-9 alone (cutoff value ≥37 unit/mL) was 63 percent sensitive for detecting cholangiocarcinoma, while the sensitivity of the combined CA 19-9/CEA index (CA 19-9 + [CEA x 40]) was only 33 percent, albeit with higher specificity [44].

Alpha-fetoprotein — All patients with a solid liver lesion should have serum AFP levels checked. If elevated, a diagnosis of HCC becomes more likely, though imaging studies and possibly biopsy (if the imaging features are not characteristic for HCC) are still required to confirm the diagnosis. The rare combined hepatocellular-cholangiocarcinoma tumors may be characterized by high levels of AFP and low levels of CA 19-9 and/or CEA [45]. (See "Clinical features and diagnosis of hepatocellular carcinoma", section on 'Imaging' and "Epidemiology, pathogenesis, and classification of cholangiocarcinoma", section on 'Combined hepatocellular-cholangiocarcinoma'.)

Serum IgG4 — IgG4-related sclerosing cholangitis may be confused with cholangiocarcinoma. The role of assaying for IgG4 in patients suspected of having cholangiocarcinoma is unclear. A serum concentration of IgG4 can be obtained if IgG4-related sclerosing cholangitis is in the differential diagnosis (eg, in a patient with autoimmune pancreatitis); however, serum IgG4 levels can also be increased in cholangiocarcinoma [46]. (See "Pathogenesis and clinical manifestations of IgG4-related disease", section on 'IgG4-related sclerosing cholangitis'.)

Imaging studies — Cholangiocarcinoma is often suspected based on ultrasound findings. Additional imaging studies (eg, CT scanning, MRI, magnetic resonance cholangiopancreatography [MRCP], endoscopic retrograde cholangiopancreatography [ERCP], endoscopic ultrasound [EUS]) are essential for confirming the diagnosis and for planning management.

Ultrasound — For patients with jaundice, the initial imaging study is typically a transabdominal ultrasound. Transabdominal ultrasound has high sensitivity for detecting biliary tract dilation and establishing the level of obstruction. The diagnostic accuracy of ultrasound was shown in a study of 429 patients who presented with obstructive jaundice over a 10-year period [47]. Ultrasound demonstrated ductal obstruction in 89 percent, and its sensitivity for localizing the site of obstruction was 94 percent.

Abdominal ultrasound is also the test of choice for most patients with right upper quadrant abdominal pain without jaundice, since its sensitivity for detecting gallstones and ability to measure biliary dilatation exceeds that of CT scanning. However, if the suspicion for cholangiocarcinoma is high, we proceed directly to cross-sectional imaging. (See 'MDCT' below and 'MRI and MRCP' below and "Diagnostic approach to the adult with jaundice or asymptomatic hyperbilirubinemia", section on 'Evaluation for intrahepatic cholestasis'.)

Specific ultrasound findings are associated with various types of cholangiocarcinoma [48] (see "Epidemiology, pathogenesis, and classification of cholangiocarcinoma", section on 'Cholangiocarcinoma'):

- Klatskin tumors (tumors involving the proper hepatic duct bifurcation (figure 1)) often appear as segmental dilatation and nonunion of the right and left ducts.
- Papillary tumors appear as polypoid intraluminal masses.
- Nodular cholangiocarcinomas appear as discrete smooth masses with associated mural thickening.
- Intrahepatic cholangiocarcinoma appears as a poorly marginated mass lesion on ultrasound. The mass may have mixed echogenicity or be predominantly hypo- or hyperechoic depending on the amount of fibrous tissue, mucin, and calcification within the tumor.

Perihilar and distal extrahepatic cancers may not be detected, especially if small, but indirect signs (ductal dilatation throughout the obstructed liver segments) may point toward the diagnosis. An obstructing lesion is suggested by ductal dilatation (>6 mm in normal adults with an intact gallbladder) in the absence of stones. Proximal lesions cause dilation of the intrahepatic ducts alone, while both intrahepatic and extrahepatic ducts are dilated with more distal lesions [19]. The location of the tumor can be suggested if there is an abrupt change in ductal diameter.

The main limitation of abdominal ultrasound is that it is often unable to visualize the distal common bile duct, which may be obscured by duodenal air. The diagnosis of distal biliary obstruction is therefore often made by the surrogate finding of biliary dilatation. Furthermore, the bile ducts may not be visibly dilated in cholangiocarcinomas with underlying PSC or cirrhosis. Nonetheless, the presence of progressive biliary dilatation in the setting of a dominant stricture or thickening of the bile duct wall in patients with PSC should raise a strong suspicion for cholangiocarcinoma [49].

An important adjunct to diagnostic ultrasound is the ability to evaluate vascular involvement (ie, compression, encasement, or thrombosis of the portal vein, encasement or occlusion of the hepatic artery) using duplex ultrasound (color Doppler). Invasion into the portal vein or hepatic artery is an important indicator of unresectability. In one study, Doppler imaging was comparable to angiography with computed tomographic arterial portography for detecting invasion of the portal vein [50]. (See "Treatment of localized cholangiocarcinoma: Adjuvant and neoadjuvant therapy and prognosis", section on 'Preoperative assessment and criteria for resectability'.)

MDCT — Because of its widespread availability, a CT scan is commonly obtained as an alternative to transabdominal ultrasound in patients with suspected biliary malignancy. It is useful for detecting intrahepatic tumors, clarifying the level of biliary obstruction, and detecting the presence of liver atrophy. Multiphasic contrast-enhanced multidetector-row CT (MDCT) can also help distinguish benign from malignant intrahepatic bile duct strictures (particularly during the portal venous phase) and visualize nodal basins [51,52].

Intrahepatic cholangiocarcinoma — The primary differential diagnosis in patients without cirrhosis is metastases from another site. When an intrahepatic lesion is noted on an imaging study in the setting of cirrhosis, the next diagnostic step is differentiation between cholangiocarcinoma and HCC. Typical radiographic features of cholangiocarcinoma include a hypodense hepatic lesion that can be either well defined or infiltrative without a capsule, with biliary dilatation. The dense fibrotic nature of the tumor may cause capsular retraction, which is seen in up to one-fifth of cases. Following contrast administration, there is peripheral (rim) enhancement throughout both arterial and venous phases [51,53]. However, these classic features were only present in 70 percent of cases in one study [54]. Some small mass-forming intrahepatic cholangiocarcinomas are arterially hyperenhancing and may mimic HCC, which hyperenhances during the arterial phase and demonstrates washout during the delayed venous phase [55]. (See "Clinical features and diagnosis of hepatocellular carcinoma", section on 'Computed tomography'.)

Some intrahepatic tumors can contain both elements of cholangiocarcinoma and HCC in the same nodule, termed mixed hepatocellular-cholangiocellular carcinomas. The imaging characteristics of combined hepatocellular-cholangiocarcinoma may be distinct on cross-sectional imaging, or they may overlap with those of HCC and cholangiocarcinoma; discriminating features such as classic enhancement patterns and biliary ductal dilatation are not universally present [56-59]. In the absence of classic imaging features and supportive information for HCC or cholangiocarcinoma, biopsy may be needed for confirmation of the diagnosis. (See "Epidemiology, pathogenesis, and classification of cholangiocarcinoma", section on 'Combined hepatocellular-cholangiocarcinoma'.)

MDCT may provide more information regarding resectability of intrahepatic cholangiocarcinoma than does MRI. As an example, the MRI and MDCT images of 20 patients with intrahepatic cholangiocarcinoma were compared [60]. The extent of tumor enhancement was similar with both imaging methods, and biliary ductal dilatation was detected in 65 percent by either method. However, the relationship of the tumor to the vessels and surrounding organs was more easily evaluated on MDCT than on MRI [60]. (See 'MRI and MRCP' below.)

Extrahepatic cholangiocarcinoma — Among patients with perihilar and distal extrahepatic cholangiocarcinoma, the site of ductal dilatation is often suggestive of the location of the obstructing lesion:

- Ductal dilatation in both hepatic lobes with a contracted gallbladder or nonunion of the right and left hepatic ducts, with or without a visibly thickened wall, suggests a Klatskin tumor.

- Because they do not cause jaundice until later in the course, tumors that arise from the right or left hepatic ducts are often large and infiltrate the surrounding hepatic parenchyma. Intrahepatic ductal dilatation and lobar or segmental atrophy of the hepatic parenchyma can suggest the site of origin.

  A distended gallbladder with dilated intrahepatic and extrahepatic ducts is more typical of tumors involving the common bile duct, ampulla of Vater, or pancreas. Although cholangiocarcinoma is less common than pancreatic carcinoma, it should be suspected in a patient with a specific risk factor (eg, PSC). (See "Epidemiology, pathogenesis, and classification of cholangiocarcinoma".)

  A distended gallbladder without dilated intrahepatic or extrahepatic ducts suggests cystic duct stones or a tumor.

Tumor staging — Findings on MDCT scan may aid with tumor staging, but there are limitations:

- Dilatation of the intrahepatic ducts within an atrophied hepatic lobe, in conjunction with a hypertrophic contralateral lobe (the atrophy-hypertrophy complex), suggests invasion of the branch portal vein [61].
- MDCT can often visualize the pertinent nodal basins [51,52]; however, the sensitivity of nodal size as a determinant of malignant involvement is low (50 percent in one study [62]). As a result, preoperative lymph node enlargement should not be deemed evidence of non-curability.
- MDCT is limited in its ability to establish the extent of intraductal tumor spread and resectability, particularly for the periductal infiltrative type of tumor [63,64]. In one report of 29 patients with histologically-proven hilar cholangiocarcinoma, all of whom underwent MDCT (arterial and portal venous phase), resectability was correctly predicted in only 60 percent [64].
- For perihilar tumors, MDCT has limited sensitivity for nodal disease that is distant to the hepatoduodenal ligament (eg, to the periaortic, pericaval, or celiac artery lymph nodes) [2] and for peritoneal metastases.
- Abdominal lymphadenopathy is a common finding in patients with PSC, and its presence on a preoperative CT scan does not necessarily indicate malignant involvement. (See "Epidemiology, pathogenesis, and classification of cholangiocarcinoma".)

MRI and MRCP — On MRI, cholangiocarcinomas appear as hypointense lesions on T1-weighted images and are heterogeneously hyperintense on T2-weighted images [65]. T2-weighted images may also show central hypointensity corresponding to areas of fibrosis. Dynamic images show peripheral enhancement followed by progressive and concentric filling in of the tumor with contrast material. Pooling of contrast on delayed images is suggestive of a peripheral cholangiocarcinoma.

Mixed hepatocellular-cholangiocellular carcinomas have a distinct appearance on MRI [20,59,66]. A strong enhancing rim and irregular shape on gadoxetic acid-enhanced MRI favors a mixed tumor, while a lobulated shape, weak rim, and a target appearance favors a mass-forming intrahepatic cholangiocarcinoma [59]. The target appearance can also help to differentiate mixed hepatocellular-cholangiocellular carcinoma from an atypical hypovascular HCC [66].

MRI combined with MRCP is a noninvasive technique for evaluating the intrahepatic and extrahepatic bile ducts and the pancreatic duct that is emerging as an excellent tool for the preoperative assessment of biliary tract cancers. Unlike conventional ERCP, MRCP does not require contrast material to be administered into the ductal system.

MRCP has advantages over MDCT, as well. In addition to imaging the liver parenchyma and intrahepatic lesions, it can create a three-dimensional image of the biliary tree (allowing assessment of the bile ducts both above and below a stricture) and vascular structures (image 1 and image 2).

MRCP provides information about disease extent and potential resectability that is at least comparable to that obtained using MDCT, cholangiography, and angiography [67-73]. In a series comparing MRCP with ERCP in 40 patients with malignant perihilar obstruction, both techniques detected 100 percent of biliary obstructions. However, MRCP was superior in definition of anatomical extent of tumor and the cause of jaundice [72].

The place of MRCP in the preoperative evaluation of suspected cholangiocarcinoma is evolving and somewhat center dependent [74,75]. Some consider that the combination of MRCP and MDCT have largely supplanted invasive cholangiography in patients with obstructive jaundice thought due to a proximal lesion [74]. However, one of the disadvantages of MRCP is that current technology does not allow any interventions to be performed, such as stone extraction, stent insertion, or biopsy. In addition, in approximately 20 percent of cases, MRCP understages disease extent [69]. Finally, MRCP requires dedicated radiology personnel and a high level of technical expertise. If at all possible, MRCP should be performed before biliary drainage since evaluation for biliary pathology is more difficult if the biliary tree is collapsed from a preceding biliary drainage.

Endoscopy and percutaneous cholangiography

Cholangiography — Cholangiography involves injection of radiographic contrast material to opacify the bile ducts; it can be performed by ERCP (image 3) or via a percutaneous approach (percutaneous transhepatic cholangiography [PTC]). Preoperative cholangiography may be indicated either diagnostically or therapeutically for patients with biliary obstruction. (See "Percutaneous transhepatic cholangiography in adults".)

Although cholangiography is important for visualizing the site and extent of biliary obstruction, other less invasive and equally accurate studies such as MRCP and MDCT scanning have largely replaced invasive cholangiography in patients thought to have a hilar cholangiocarcinoma in centers with expertise in this technique [74]. However, cholangiography may still be indicated if the suspected level of obstruction is distal or if preoperative drainage of the biliary tree is

needed. In addition, many surgeons still rely on images from ERCP or PTC rather than MRCP to determine resectability. (See "Treatment of localized cholangiocarcinoma: Adjuvant and neoadjuvant therapy and prognosis", section on 'Preoperative assessment and criteria for resectability'.)

The choice of modality depends in part upon the level of endoscopic or radiologic expertise available to the clinician. However, ERCP is preferred in patients with PSC since the marked stricturing of the intrahepatic biliary tree makes a percutaneous approach difficult. Conversely, PTC is generally preferred for imaging the more proximal biliary system if there is complete obstruction of the distal biliary tract. (See "Percutaneous transhepatic cholangiography in adults" and "Primary sclerosing cholangitis in adults: Management", section on 'Gallbladder carcinoma and cholangiocarcinoma'.)

In the past, a presumptive diagnosis of sclerosing cholangiocarcinoma was often made when a focal stenotic lesion was visualized by cholangiography in a jaundiced patient. However, the inaccuracy of this approach was shown in a series of 98 consecutive patients in whom a diagnosis other than sclerosing cholangiocarcinoma was made at surgery in 31 percent [27]. There were five papillary cholangiocarcinomas, 12 gallbladder carcinomas that invaded the bile duct, five metastatic tumors to the bile duct, and six benign lesions (three granulomas and three cases of idiopathic benign focal stenosis).

If needed, bile samples or brush cytology can be obtained during ERCP or PTC (see 'Need for tissue diagnosis' above). Sampling of bile by PTC or ERCP alone will result in positive cytology in approximately 30 percent of cases of cholangiocarcinoma [76,77]. The diagnostic yield is increased if the lesion in question is biopsied or brushings are taken from the duct for cytologic examination. Unfortunately, endoscopic brush cytology in patients who have clinical and/or radiographic findings suggestive of malignancy has a limited sensitivity (35 to 69 percent), and the addition of endoscopic biopsy of malignant strictures increases this value only to 43 to 88 percent [78-82]. These tests may be useful in the diagnostic evaluation if they are positive, but a negative test cannot rule out malignant disease.

Combining brush cytology with tumor marker assessment may provide better diagnostic accuracy. In a previously described study, the combination of a positive brush cytology or an abnormal CA 19-9 had a sensitivity and specificity of 88 percent (95% CI 50-99 percent) and 97 percent (95% CI 86-100 percent), respectively [34]. (See 'Tumor markers' above.)

Fluorescence in situ hybridization (FISH) is a cytologic test using labeled deoxyribonucleic acid (DNA) probes to detect abnormal loss or gain of chromosomes or chromosomal loci that may

also improve the sensitivity of brush cytology [83]. (See "Tools for genetics and genomics: Cytogenetics and molecular genetics".)

Once instrumentation of the biliary tree has been accomplished, an endoprosthesis can be placed to provide biliary drainage, thus reducing the risk of infection and cholangitis. (See "Treatment of localized cholangiocarcinoma: Adjuvant and neoadjuvant therapy and prognosis", section on 'Preoperative assessment and criteria for resectability'.)

Endoscopic ultrasound — For distal bile duct lesions, EUS can visualize the local extent of the primary tumor and the status of regional lymph nodes. EUS-guided fine needle aspiration (FNA) of tumors and enlarged lymph nodes can also be performed. EUS with FNA has a greater sensitivity for detecting malignancy in distal tumors than does ERCP with brushings [84]. This technique also avoids contamination of the biliary tree, which can occur with ERCP.

One series included 73 patients with either pancreatic carcinoma (n = 54) or cholangiocarcinoma (n = 19), all of whom underwent preoperative EUS, transabdominal ultrasound, CT, and angiography [85]. EUS was significantly more sensitive for the detection of the cancer (96 percent) than ultrasound (81 percent), CT (86 percent), or angiography (59 percent). For diagnosing portal venous invasion, EUS was more sensitive (95 percent) and accurate (93 percent) than ultrasound (55 and 67 percent), CT (65 and 95 percent), and angiography (75 and 79 percent).

The sensitivity of EUS for imaging and staging proximal bile duct lesions is less than for distal lesions, and clinical experience is limited [86,87].

Intraductal ultrasound — Intraductal ultrasound (IDUS) can help distinguish benign from malignant strictures based upon bile duct anatomy and unique sonographic imaging characteristics (image 4). In addition, IDUS can improve the accuracy of local tumor staging of bile duct carcinomas. IDUS detects early lesions, determines the longitudinal tumor extent, and identifies tumor extension into adjacent organs and major blood vessels with a diagnostic accuracy of nearly 100 percent [88-91]. In particular, IDUS can accurately identify tumor invasion into the pancreatic parenchyma [89,90,92], portal vein [88,90,92,93], and right hepatic artery [90-92,94]. (See "Intraductal ultrasound for evaluating the pancreaticobiliary ductal system".)

In contrast to EUS, IDUS is often better able to evaluate the proximal biliary system and surrounding structures, such as the right hepatic artery, portal vein, and the hepatoduodenal ligament (image 5 and image 6). Examination of more distant tissues is hindered by its limited depth of penetration [88,89,92,94]. IDUS may also have limited value in evaluating lymph nodes, and unlike EUS, IDUS cannot be used to perform FNA.

Cholangioscopy — Cholangioscopy (direct visualization of the bile ducts using a very thin cholangioscope) can be used to evaluate indeterminate biliary strictures (ie, strictures that could not be diagnosed as being benign or malignant with sampling techniques such as brush cytology or biopsy) (image 7 and image 8 and image 9 and picture 5 and picture 6) [95-104]. During cholangioscopy, targeted biopsies of bile duct lesions can be obtained (picture 7). It can also be used to evaluate equivocal fluoroscopy findings during ERCP, to assess the extent of cholangiocarcinoma prior to surgery, and to identify stones not seen by conventional cholangiography. (See "Cholangioscopy and pancreatoscopy".)

Cholangioscopic visualization of the bile duct in a patient with cholangiocarcinoma may show "tumor vessels" (irregularly dilated and tortuous blood vessels) (picture 8 and picture 9). Other findings associated with malignancy include intraductal nodules or masses, infiltrative or ulcerated strictures, and papillary or villous mucosal projections [105].

PET scan — The place of positron emission tomography with fluorodeoxyglucose (FDG-PET) scanning in the staging evaluation of patients with cholangiocarcinoma is evolving. Although PET and integrated PET/CT do not add information over other modalities such as MDCT or MRI/MRCP for staging the primary tumor, the available evidence suggests that preoperative PET scanning leads to a change in surgical management in approximately one-fourth of cases, mainly by detecting occult distant metastatic disease. Although preoperative PET scanning is not recommended in consensus-based guidelines from the National Comprehensive Cancer Network (NCCN) [106], we suggest a PET scan prior to diagnostic laparoscopy for operable patients who appear to have potentially resectable cholangiocarcinoma after the initial radiographic evaluation.

FDG-PET permits visualization of cholangiocarcinomas because of the high glucose uptake of bile duct epithelium. The majority of biliary tract tumors are FDG-avid [107]. PET and integrated PET/CT can detect nodular cholangiocarcinomas as small as 1 cm, but they are less helpful for infiltrating tumors, which may not accumulate FDG [108-111]. There are no specific advantages of PET or integrated PET/CT over MDCT or MRI/MRCP in the diagnosis of the primary tumor.

PET scanning appears to have of greater utility for identifying occult metastases [107,109-115]:

- In one series, performance of a preoperative PET scan altered surgical management in 11 of 36 patients (31 percent), mainly because of detection of unsuspected metastases [110]. However, sensitivity for extrahepatic metastases was only 50 percent.

- In another report of 123 patients with suspected cholangiocarcinoma who had undergone MDCT and MRI/MRCP, integrated PET/CT detected 7 of the 12 cases of distant metastases whereas MDCT detected none (sensitivity 58 versus 0 percent). The sites of metastatic

disease were bone (n = 2), peritoneum (n = 2), liver (n = 2), and extra-abdominal lymph nodes (n = 2) [115]. Even with PET/CT, four cases of peritoneal metastases and one case of liver metastasis were not detected.

Given its limitations in sensitivity, PET is not an adequate replacement for diagnostic laparoscopy. (See 'Staging laparoscopy' above.)

Another possible role for PET is in screening patients with PSC for the presence of cholangiocarcinoma [116-120]. In one retrospective report, PET scans were performed in nine patients with PSC, six with PSC and known cholangiocarcinoma, and five controls [116]. PET scan correctly identified "hot spots" in each of the patients with cholangiocarcinoma and none in the other groups.

However, the possibility of acute cholangitis (or other benign lesion) causing a false-positive study has to be considered, particularly in patients with PSC [110]. Inflammatory lesions accumulate FDG, but uptake is generally less than it is with malignant lesions. Semiquantitative analysis of the maximal Standardized Uptake Value (SUVmax) or tumor to normal liver activity ratio (T/N ratio) can be used to differentiate benign from malignant lesions [116,119,121]. However, the optimal cutoff to distinguish benign versus malignant lesions not been established. Some reports consider that SUVmax threshold values >3.5 to 3.6 are a useful discriminator [108,122,123], but higher cutoff values enhance sensitivity at the expense of specificity.

As an example, a retrospective series of 65 patients with PSC who were suspected of having cholangiocarcinoma and underwent integrated PET/CT, follow-up, and histopathology revealed cholangiocarcinoma in 47 [119]. Cholangiocarcinomas had SUVmax values ranging from 2.7 to 20.9 (mean 8 ± 2.9), whereas benign lesions had SUVmax values ranging from 1.7 to 5.7 (mean 3 ± 1). Applying the SUVmax threshold of 3.6 to this series would have resulted in six benign lesions being misclassified as tumors.

Chest CT — Consensus-based guidelines from the NCCN [106]suggest that all patients without documented intraabdominal metastases who are potential surgical candidates undergo CT scan of the chest. However, in our view, integrated PET/CT is preferred as it allows detection of occult metastatic disease outside of the chest. One disadvantage of integrated PET/CT is that the CT scan is done without contrast at most institutions, and this can limit the ability to detect small mediastinal lymph nodes.

Angiography — Angiography can accurately document vascular encasement or thrombosis of the portal vein and hepatic artery. However, with the advent of MDCT and MRCP, it is rarely necessary before surgery.

SUMMARY AND RECOMMENDATIONS

- **Definition** – The term cholangiocarcinoma is used to designate bile duct cancers arising in the intrahepatic, perihilar, or distal (extrahepatic) biliary tree, exclusive of the gallbladder or ampulla of Vater (figure 1). (See 'Terminology' above.)

- **Clinical presentation**

  - Most patients with extrahepatic cholangiocarcinoma present with painless jaundice, right upper quadrant abdominal pain, and weight loss. Patients with intrahepatic cholangiocarcinoma are less likely to be jaundiced.

  - The development of cholangiocarcinoma in a patient with primary sclerosing cholangitis (PSC) is often heralded by rapid clinical deterioration with declining performance status, in addition to jaundice, weight loss, and abdominal pain. (See 'Clinical presentation' above.)

- **Diagnostic approach**

  - The initial study is often a cross sectional imaging study, such as MRI/magnetic resonance cholangiopancreatography (MRCP) or a multiphasic contrast-enhanced multidetector-row computed tomography (MDCT). Imaging test findings associated with different tumor locations include:

    - **Distal extrahepatic cholangiocarcinoma** – Intrahepatic and extrahepatic ductal dilation. An abrupt change in ductal diameter may be seen.

    - **Perihilar cholangiocarcinoma** – Intrahepatic ductal dilatation with normal-caliber extrahepatic ducts.

    - **Intrahepatic cholangiocarcinoma** – Mass lesion, usually in a noncirrhotic liver.

  - All patients with suspected cholangiocarcinoma should have tumor markers (carbohydrate antigen 19-9 [CA 19-9], carcinoembryonic antigen [CEA], and for patients with intrahepatic lesions, alpha-fetoprotein [AFP]) checked. Elevated tumor markers may support a diagnosis of cholangiocarcinoma or, in the case of an elevated AFP, suggest an alternative diagnosis (hepatocellular carcinoma). They may also be helpful in monitoring patients for recurrence after therapy. (See 'Tumor markers' above.)

    For patients with PSC, we typically use a CA 19-9 cutoff value of ≥129 unit/mL to increase suspicion for a cholangiocarcinoma, especially in the presence of a dominant

hilar stricture. (See 'CA 19-9' above.)

- The subsequent diagnostic approach varies depending on the location of the suspected lesion, based on initial imaging (distal extrahepatic, perihilar, or intrahepatic (figure 1)), and whether or not the patient has a history of PSC (algorithm 1 and algorithm 2). However, even after extensive diagnostic workup, surgical exploration may be required to confirm the diagnosis. (See 'Diagnostic approach' above.)

  - **Distal extrahepatic lesion** – Endoscopic ultrasound (EUS) or endoscopic retrograde cholangiopancreatography (ERCP) is preferred as the next step in the evaluation, as the studies permit direct visualization of the area of abnormality, enable a biopsy (either fine-needle aspiration [FNA] or brush cytology), and in the case of ERCP, allow for the possibility of therapeutic intervention (eg, stent placement). We prefer EUS unless the patient requires endoscopic drainage or the lesion is not amenable to EUS-guided FNA because of its location. (See 'Suspected distal extrahepatic cholangiocarcinoma' above and 'Endoscopy and percutaneous cholangiography' above.)

  - **Perihilar lesion** – If MRCP/MDCT fails to confirm the diagnosis, additional imaging with ERCP is the next step. (See 'Suspected perihilar cholangiocarcinoma' above and 'MRI and MRCP' above and 'MDCT' above.)

  - **Intrahepatic lesion** – Findings on cross-sectional imaging (MDCT scan or MRI) can differentiate between cholangiocarcinoma and hepatocellular carcinoma, provided the patient is not known to have or suspected of having an extrahepatic malignancy, in which case metastatic disease should be ruled out first. If the initial imaging test is nondiagnostic, the other imaging modality (CT or MRI) can then be obtained. (See 'Suspected intrahepatic cholangiocarcinoma' above and "Approach to the adult patient with an incidental solid liver lesion", section on 'Diagnostic approach'.)

  - **Patients with PSC** – For patients with PSC, an MRCP should be done, if not done previously, to document the segmental extent of ductal involvement, search for intrahepatic metastases, and identify aberrant ductal anatomy (algorithm 2). If the MRCP is nondiagnostic or if a dominant stricture is identified, we obtain an ERCP with brush cytology (with or without intraductal ultrasound [IDUS]). (See 'Patients with primary sclerosing cholangitis' above.)

    If both of these tests are nondiagnostic, we suggest positron emission tomography (PET) scan. (See 'PET scan' above.)

- The necessity of establishing a tissue diagnosis prior to surgery depends upon the clinical situation. It is not critical for planning surgery in patients with characteristic findings of malignant biliary obstruction and may not be necessary for planning palliative therapy, such as biliary drainage, in unresectable cases. In addition, FNA or CT/MRI-guided biopsy can rarely result in seeding of the biopsy tract with malignant cells, which may preclude an otherwise eligible transplantation candidate from undergoing transplantation. Therefore, in patients with perihilar tumors, the case should be discussed with the transplantation team prior to proceeding with tissue sampling. (See 'Need for tissue diagnosis' above.)

- **Staging and the staging workup** – Separate tumor, node, metastasis (TNM) staging classifications are available for distal, perihilar, and intrahepatic cholangiocarcinomas (table 1 and table 2 and table 3). (See 'Tumor staging' above.)

  - The preoperative staging evaluation starts with radiographic and endoscopic studies, some of which may have already been done as part of the diagnostic evaluation (see 'The staging workup' above):

    - We perform MDCT scanning of the abdomen and pelvis, with or without MRCP.

    - If there is no evidence of distant metastatic disease, extraregional lymph node involvement, or invasion of critical adjacent structures and if the patient is a good surgical candidate, we suggest a PET scan. If the PET scan is normal and the patient is a good surgical candidate, we proceed with laparoscopy. (See 'PET scan' above.)

    - If additional information is needed to determine if there is extraregional lymph node involvement or invasion of adjacent structures, we will typically obtain an EUS (with or without IDUS), particularly for distal bile duct lesions, or ERCP, if preoperative drainage of the biliary tree is needed.

    - If needed, duplex ultrasound (color Doppler) can be used to evaluate for vascular involvement, an important indicator of resectability.

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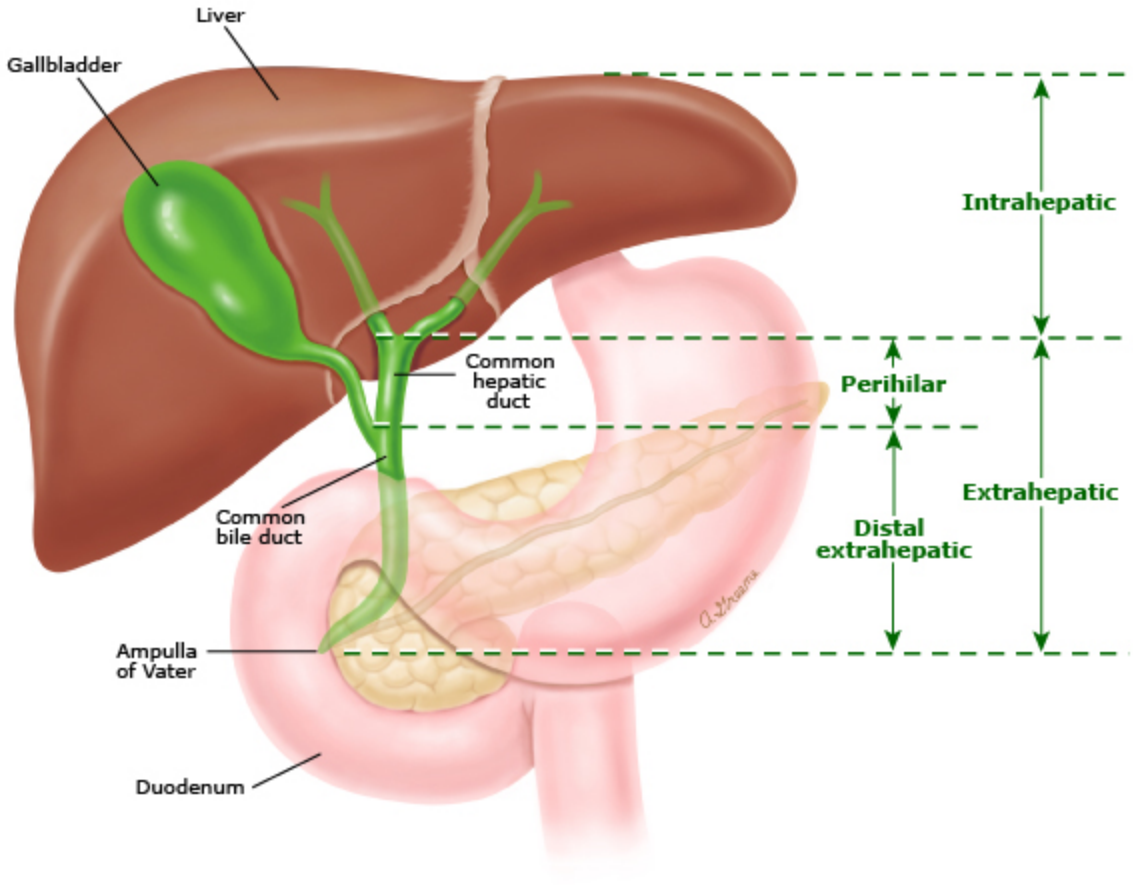
Topic 2500 Version 34.0

GRAPHICS

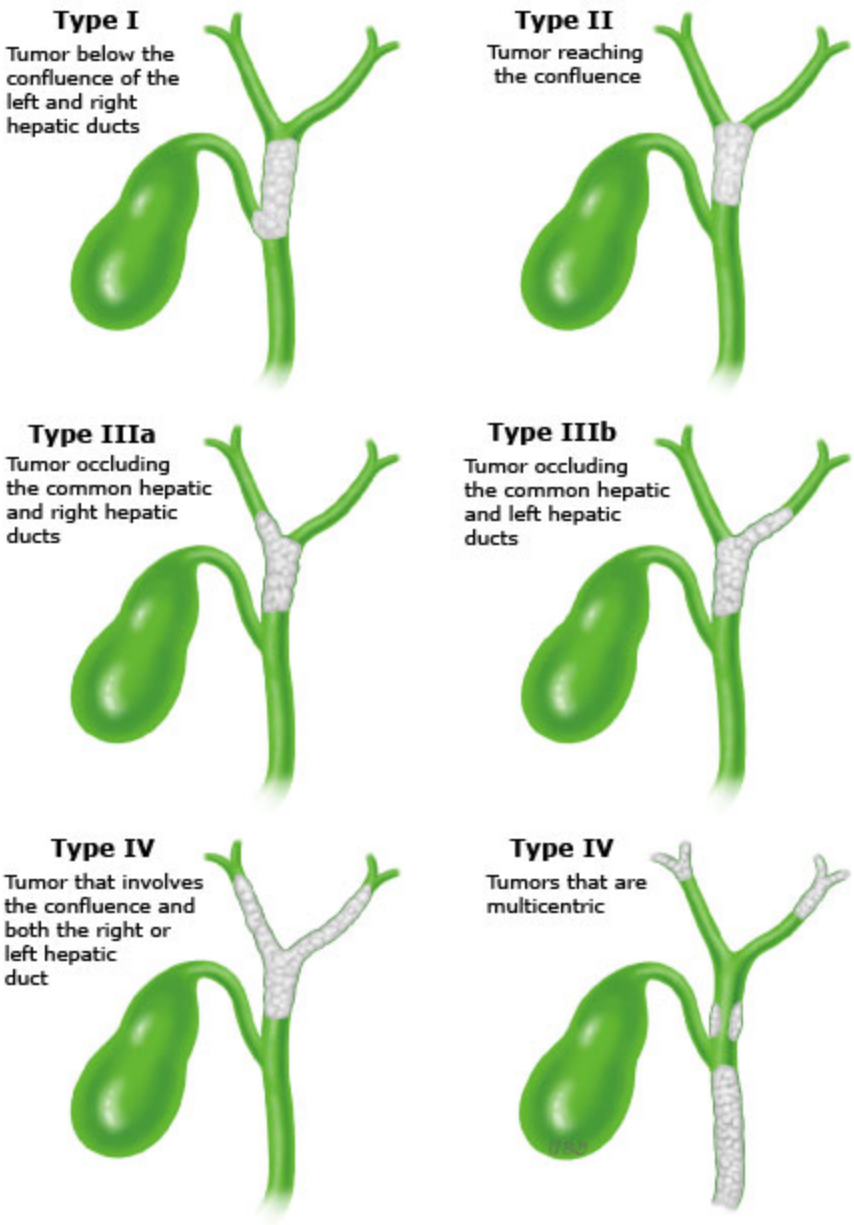
Anatomic classification of cancers of the human biliary tract



Classifications defined by: American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th Edition, Amin MB (Ed), Chicago: Springer Science+Business Media, LLC, 2017.

Graphic 52489 Version 6.0

Bismuth-Corlette classification of biliary tract cancers

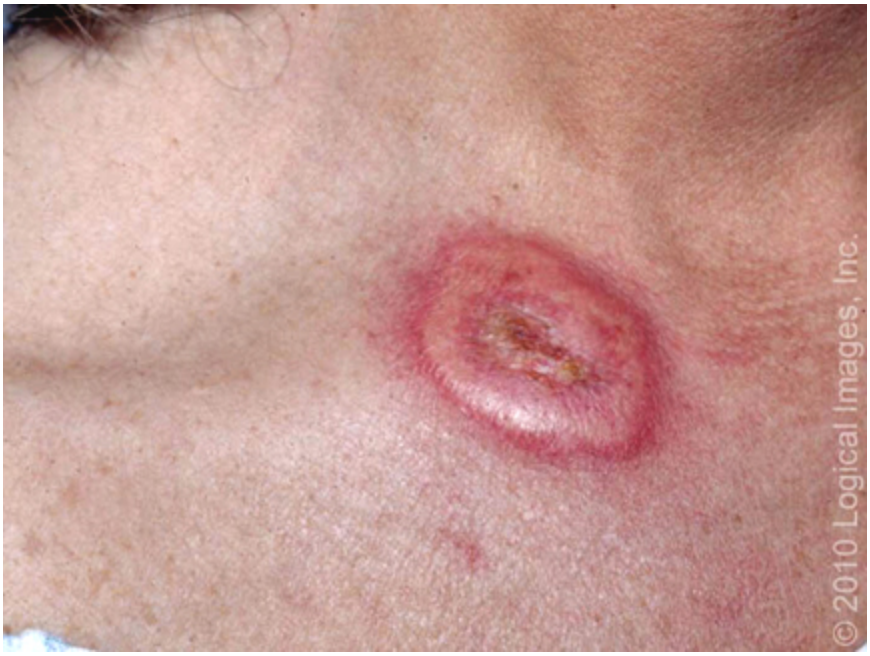


The Bismuth-Corlette classification of biliary tract. White areas represent tumor and green areas normal bile duct.

Modified from de Groen PC, Gores GJ, LaRusso NF, et al. N Engl J Med 1999; 341:1368.

Graphic 75886 Version 5.0

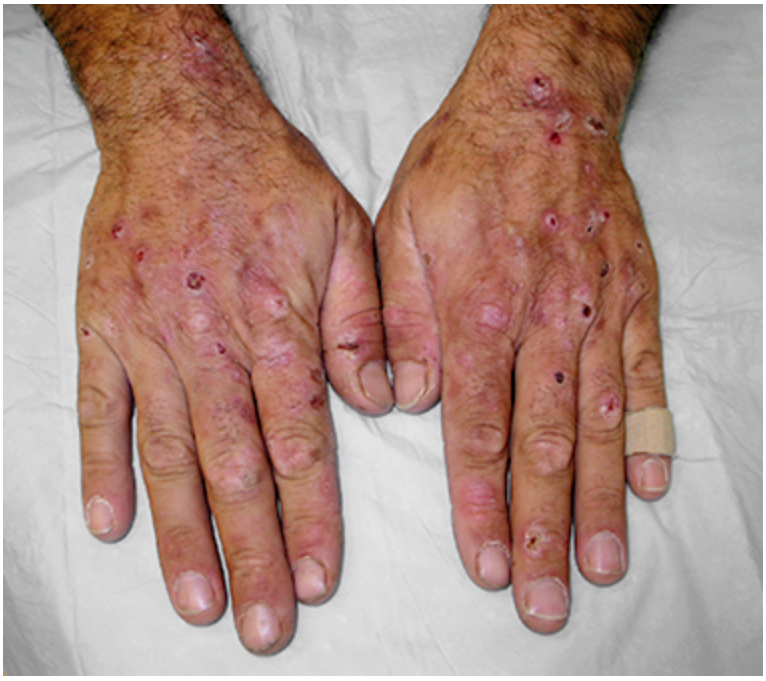
Sweet syndrome



A brightly erythematous plaque with a pustular component is visible on this patient with Sweet syndrome.

Graphic 74393 Version 6.0

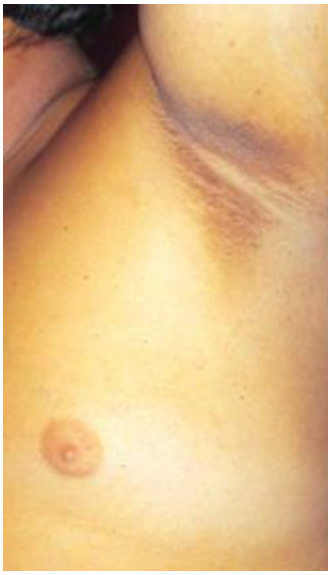
Porphyria cutanea tarda



Macular erythema, erosions, crusts, and scars are present on the hands of this patient with porphyria cutanea tarda.

Graphic 78547 Version 2.0

Acanthosis nigricans

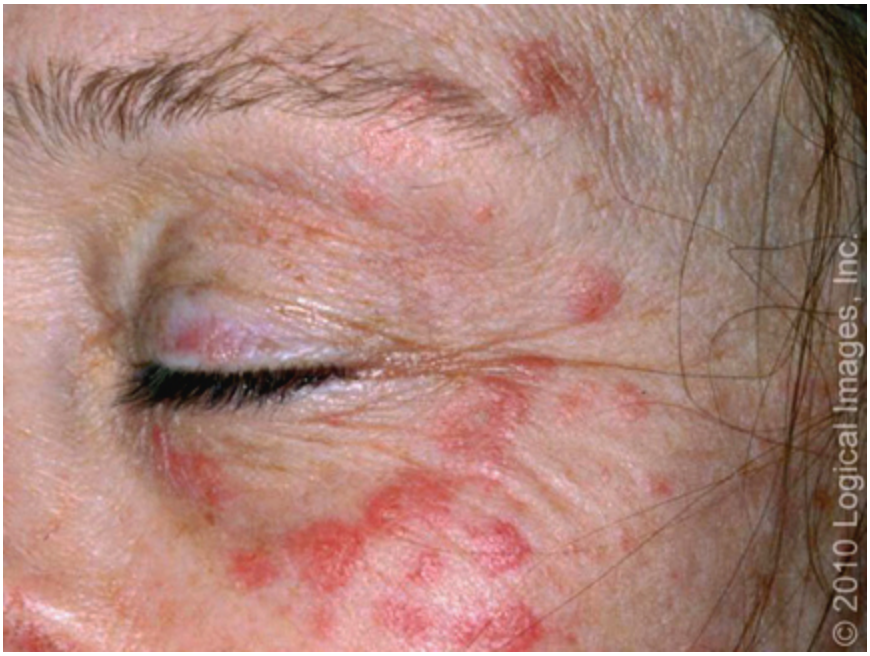


Classic hyperpigmented axillary lesion in acanthosis nigricans.

Courtesy of Jeffrey Flier, MD.

Graphic 53776 Version 3.0

Erythema multiforme



This patient with erythema multiforme presented with nontargetoid, erythematous papules on the face.

Graphic 65570 Version 6.0

Approach to the diagnosis of cholangiocarcinoma in a patient who does not ha primary sclerosing cholangitis (PSC)

CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; AFP: alpha-fetoprotein; US: ultrasound; CT: computed tomography; MRI: magnetic resonance imaging; MRCP: magnetic resonance cholangiopancreatography; MDCT: contrast-enhanced multiphasic multidetector row computed tomography; CCA: cholangiocarcinoma; EUS: endoscopic ultrasound; FNA: fine needle aspiration; ERCP: endoscopic retrograde cholangiopancreatography; PET: positron emission tomography; IDUS: intraductal ultrasound; PTC: percutaneous transhepatic cholangiography.

* A diagnosis of CCA should be considered if there are signs of biliary obstruction (eg, jaundice, abnormal liver tests in a cholestatic pattern, bile duct dilation on imaging studies) without an alternative explanation (eg, choledocholithiasis, a pancreatic head lesion). The diagnosis should also be considered in patients with an isolated intrahepatic mass on imaging and a normal serum level of AFP.

¶ All patients with suspected CCA should have tumor markers (CA 19-9, CEA, and for patients with intrahepatic lesions, AFP) checked. Elevated tumor markers may support a diagnosis of CCA or, in the case o an elevated AFP, suggest an alternative diagnosis (hepatocellular carcinoma). CA 19-9 is elevated if it is >37 units/mL.

Δ If at any point during the evaluation an alternative diagnosis is made, treatment should be instituted as appropriate for that diagnosis.

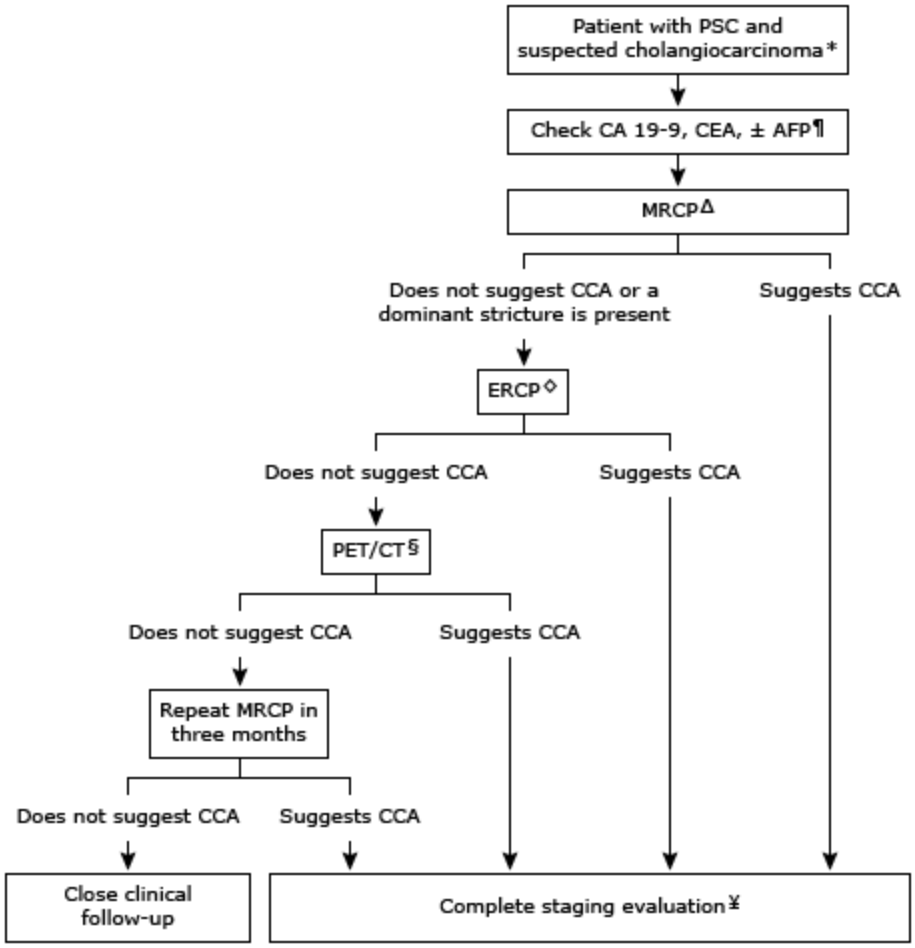
◇ If the patient is a surgical candidate. Preoperative PET/CT scan is of utility primarily for identifying occult metastases.

§ EUS is preferred in many centers for patients with extrahepatic bile duct dilation unless drainage is required or tissue cannot be obtained with FNA. For patients with a perihilar mass or isolated intrahepatic bile duct dilation, ERCP is the next test obtained since the lesion may not be visualized on EUS.

¥ With brushings/biopsies of any intraductal lesions or strictures. Obstructing lesions can be stented if needed. If ERCP is nondiagnostic, consider cholangioscopy (if available) for direct visualization of the bile duct and biopsies. IDUS (if available) can be used to further define the extent of the tumor. If the lesion is nc accessible endoscopically, consider PTC.

Graphic 96374 Version 4.0

Approach to the diagnosis of cholangiocarcinoma in a patient with primary sclerosing cholangitis



PSC: primary sclerosing cholangitis; CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; AFP: alpha-fetoprotein; MRCP: magnetic resonance cholangiopancreatography; CCA: cholangiocarcinoma; ERCP: endoscopic retrograde cholangiopancreatography; PET: positron emission tomography; CT: computed tomography; IDUS: intraductal ultrasound; PTC: percutaneous transhepatic cholangiography.

* In patients with PSC, CCA should be considered if there is rapid clinical deterioration with jaundice, weight loss, and abdominal pain. The presence of progressive biliary dilatation in the setting of a dominant stricture or thickening of the bile duct wall should also raise a strong suspicion of CCA. CCA should also be considered if suggested by screening test results (ie, CA 19-9 and/or MRCP).

¶ All patients suspected of having CCA should have tumor markers (CA 19-9, CEA, and for patients with intrahepatic lesions, AFP) checked. Elevated tumor markers may support a diagnosis of CCA or, in the case of an elevated AFP, suggest an alternative diagnosis (hepatocellular carcinoma). In patients with PSC, the optimal CA 19-9 cutoff (providing

optimal balance between sensitivity and specificity) is approximately 100 to 129 units/mL.

Δ If at any point during the evaluation, an alternative diagnosis is made, treatment should be instituted as appropriate for that diagnosis.

◇ With brushings/biopsies of any intraductal lesions or strictures. Obstructing lesions can be stented if needed. If ERCP is nondiagnostic, consider cholangioscopy (if available) for direct visualization of the bile duct and biopsies. IDUS (if available) can be used to further define the extent of the tumor. If the lesion is not accessible endoscopically, consider PTC.

§ If the diagnosis of CCA is strongly suspected but imaging has been nondiagnostic. Preoperative PET/CT scan may also help guide surgery by identifying areas more likely to harbor malignancy.

¥ If the patient is a surgical candidate.

Graphic 96373 Version 4.0

Distal bile duct cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*/high-grade dysplasia
T1	Tumor invades the bile duct wall with a depth less than 5 mm
T2	Tumor invades the bile duct wall with a depth of 5 to 12 mm
T3	Tumor invades the bile duct wall with a depth greater than 12 mm
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes
Distant metastasis (M)	
M category	**M criteria**

M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	I
T1	N1	M0	IIA
T1	N2	M0	IIIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T2	N2	M0	IIIA
T3	N0	M0	IIB
T3	N1	M0	IIB
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	Any N	M1	IV

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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Graphic 110943 Version 7.0

Perihilar bile duct cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*/high-grade dysplasia
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue, or tumor invades adjacent hepatic parenchyma
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades the main portal vein or its branches bilaterally, or the common hepatic artery; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three positive lymph nodes typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes
N2	Four or more positive lymph nodes from the sites described for N1
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups			
When T is…	**And N is…**	**And M is…**	**Then the stage group is…**
Tis	N0	M0	0

T1	N0	M0	I
T2a-b	N0	M0	II
T3	N0	M0	IIIA
T4	N0	M0	IIIB
Any T	N1	M0	IIIC
Any T	N2	M0	IVA
Any T	Any N	M1	IVB

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110944 Version 8.0

Intrahepatic bile duct cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* (intraductal tumor)
T1	Solitary tumor without vascular invasion, ≤5 cm or >5 cm
T1a	Solitary tumor ≤5 cm without vascular invasion
T1b	Solitary tumor >5 cm without vascular invasion
T2	Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral peritoneum
T4	Tumor involving local extrahepatic structures by direct invasion
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis present

Prognostic stage groups			
When T is…	**And N is…**	**And M is…**	**Then the stage group is…**
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II
T3	N0	M0	IIIA
T4	N0	M0	IIIB

Any T	N1	M0	IIIB
Any T	Any N	M1	IV

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110945 Version 7.0

Classification of jaundice according to type of bile pigment and mechanism

Unconjugated hyperbilirubinemia
Increased bilirubin production*
Extravascular hemolysis
Extravasation of blood into tissues
Intravascular hemolysis
Dyserythropoiesis
Wilson disease
Impaired hepatic bilirubin uptake
Heart failure
Portosystemic shunts
Some patients with Gilbert syndrome
Certain drugs¶ – Rifampin, probenecid, flavaspadic acid, bunamiodyl
Impaired bilirubin conjugation
Crigler-Najjar syndrome types I and II
Gilbert syndrome
Neonates
Hyperthyroidism
Ethinyl estradiol
Liver diseases – Chronic hepatitis, advanced cirrhosis
Conjugated hyperbilirubinemia
Defect of canalicular organic anion transport
Dubin-Johnson syndrome
Defect of sinusoidal reuptake of conjugated bilirubin
Rotor syndrome

Conjugated hyperbilirubinemia (continued)
Extrahepatic cholestasis (biliary obstruction)
Choledocholithiasis
Intrinsic and extrinsic tumors (eg, cholangiocarcinoma, pancreatic cancer)
Primary sclerosing cholangitis
AIDS cholangiopathy
Acute and chronic pancreatitis
Strictures after invasive procedures
Certain parasitic infections (eg, *Ascaris lumbricoides*, liver flukes)
Intrahepatic cholestasis
Viral hepatitis
Alcohol-associated hepatitis
Non-alcohol-associated steatohepatitis
Chronic hepatitis
Primary biliary cholangitis
Drugs and toxins (eg, alkylated steroids, chlorpromazine, herbal medications [eg, Jamaican bush tea], arsenic)
Sepsis and hypoperfusion states
Infiltrative diseases (eg, amyloidosis, lymphoma, sarcoidosis, tuberculosis)
Total parenteral nutrition
Postoperative cholestasis
Following organ transplantation
Hepatic crisis in sickle cell disease
Pregnancy
End-stage liver disease

AIDS: acquired immunodeficiency syndrome.

* Serum bilirubin concentration is usually less than 4 mg/dL (68 mmol/L) in the absence of underlying liver disease.

¶ The hyperbilirubinemia induced by drugs usually resolves within 48 hours after the drug is discontinued.

Graphic 55607 Version 13.0

Causes of abdominal pain by location

Right upper quadrant
Hepatitis
Cholecystitis
Cholangitis
Biliary colic
Pancreatitis
Budd-Chiari syndrome
Pneumonia/empyema pleurisy
Subdiaphragmatic abscess
Right lower quadrant
Appendicitis
Salpingitis
Ectopic pregnancy
Inguinal hernia
Nephrolithiasis
Inflammatory bowel disease
Mesenteric adenitis (yersina)
Epigastric
Peptic ulcer disease
Gastroesophageal reflux disease
Gastritis
Pancreatitis
Myocardial infarction
Pericarditis
Ruptured aortic aneurysm
Periumbilical
Early appendicitis
Gastroenteritis
Bowel obstruction

Left upper quadrant
Splenic abscess
Splenic infarct
Gastritis
Gastric ulcer
Pancreatitis
Left lower quadrant
Diverticulitis
Salpingitis
Ectopic pregnancy
Inguinal hernia
Nephrolithiasis
Irritable bowel syndrome
Inflammatory bowel disease
Diffuse
Gastroenteritis
Mesenteric ischemia
Metabolic (eg, DKA, porphyria)
Malaria
Familial Mediterranean fever
Bowel obstruction
Peritonitis
Irritable bowel syndrome

Ruptured aortic aneurysm

DKA: diabetic ketoacidosis.

Graphic 70233 Version 4.0

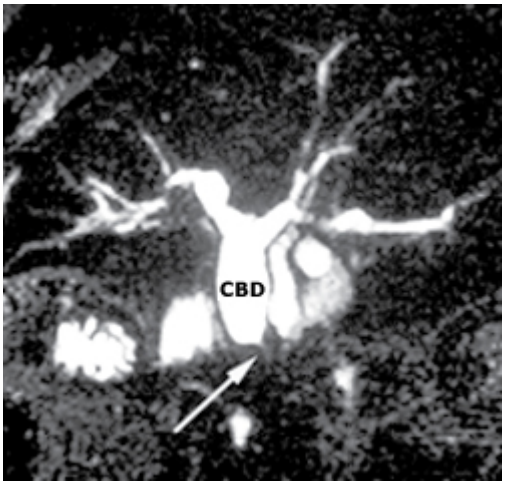
Conditions associated with increased serum levels of the tumor marker CA 19-9

Malignant
Pancreatic exocrine and neuroendocrine cancers
Biliary cancer (gallbladder, cholangiocarcinoma, ampullary cancers)
Hepatocellular cancer
Gastric, ovarian, colorectal cancer (less often)
Lung, breast, uterine cancer (rare)
Benign
Acute cholangitis
Cirrhosis and other cholestatic diseases (including gallstones)

CA 19-9: carbohydrate antigen 19-9.

Graphic 52557 Version 3.0

Distal cholangiocarcinoma as seen on MRCP

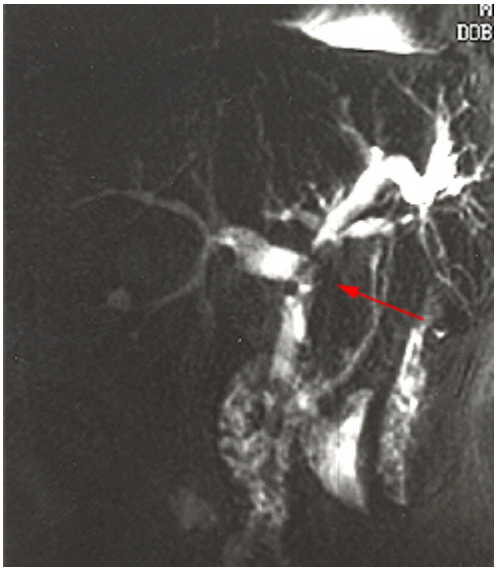


This magnetic resonance cholangiopancreatography (MRCP) image, obtained without having to opacify the bile ducts, demonstrates a circumferential narrowing of the distal common bile duct (CBD, arrow) due to a focal distal cholangiocarcinoma. The obstructing tumor is causing dilation of the CBD.

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 73964 Version 3.0

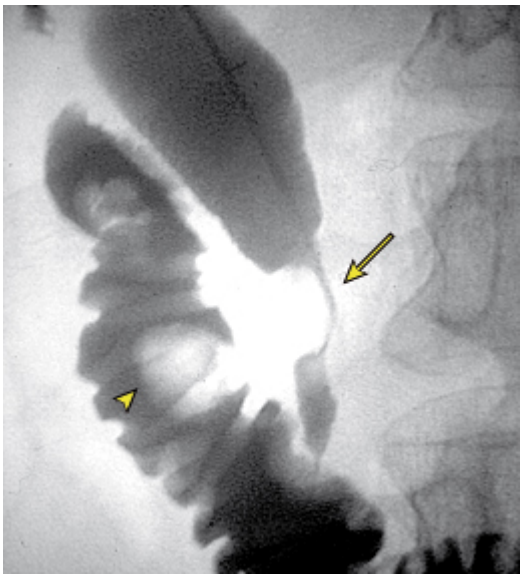
Hilar cholangiocarcinoma as seen on MRCP



This magnetic resonance cholangiopancreatography (MRCP) image depicts an intrabiliary filling defect (arrow) due to a hilar papillary cholangiocarcinoma.

Graphic 72880 Version 3.0

Cholangiocarcinoma of the common bile duct, as seen during an ERCP procedure

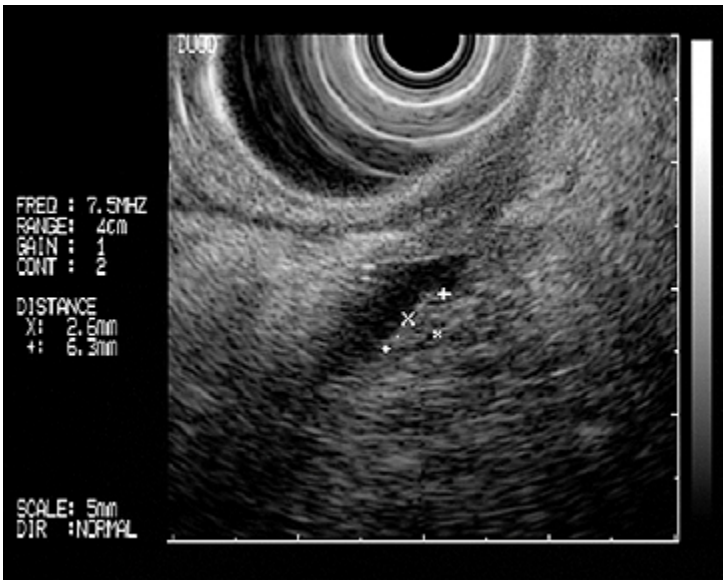


Following administration of contrast material into the biliary system and duodenum during an endoscopic retrograde cholangiopancreatography (ERCP) examination (black), circumferential narrowing of the distal common bile duct is produced by a cholangiocarcinoma (arrow). The tumor is causing proximal bile duct dilatation and is also extending into the adjacent duodenum (arrowhead), producing a C-shaped eccentric impression.

Courtesy of Jonathan Kruskal, MD.

Graphic 75950 Version 4.0

Intraductal ultrasound demonstrating a polypoid mass in the common bile duct

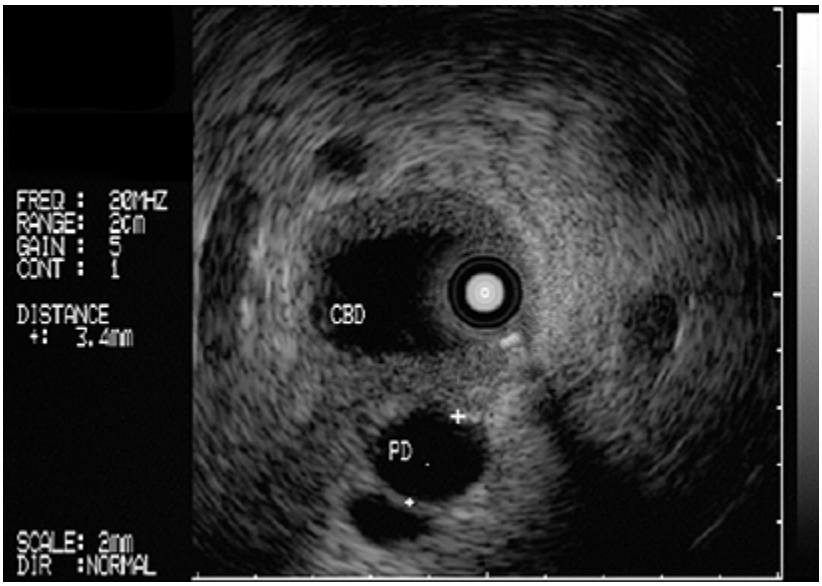


Polypoid mass within the distal common bile duct as seen by endoscopic ultrasound.

Courtesy of Drs. Michael J Levy, Enrique Vazquez-Sequeiros, and Maurits J Wiersema.

Graphic 80227 Version 5.0

Intraductal ultrasound demonstrating a normal common bile duct and pancreatic duct

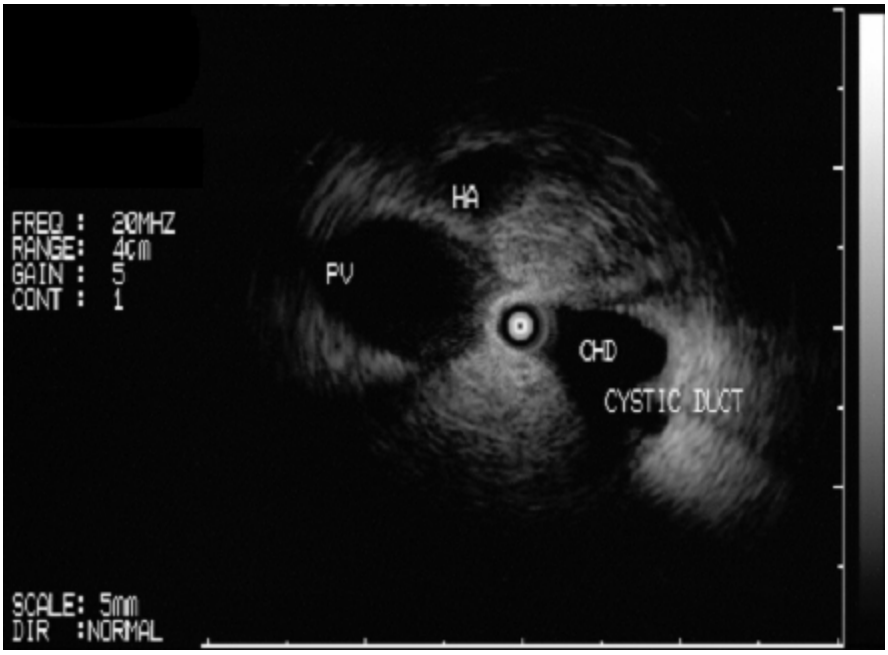


Normal intraductal ultrasound examination demonstrating the common bile duct (CBD) and pancreatic duct (PD).

Courtesy of Drs. Michael J Levy, Enrique Vazquez-Sequeiros, and Maurits J Wiersema.

Graphic 61520 Version 4.0

Intraductal ultrasound showing a normal common hepatic duct, cystic duct, portal vein, and hepatic artery

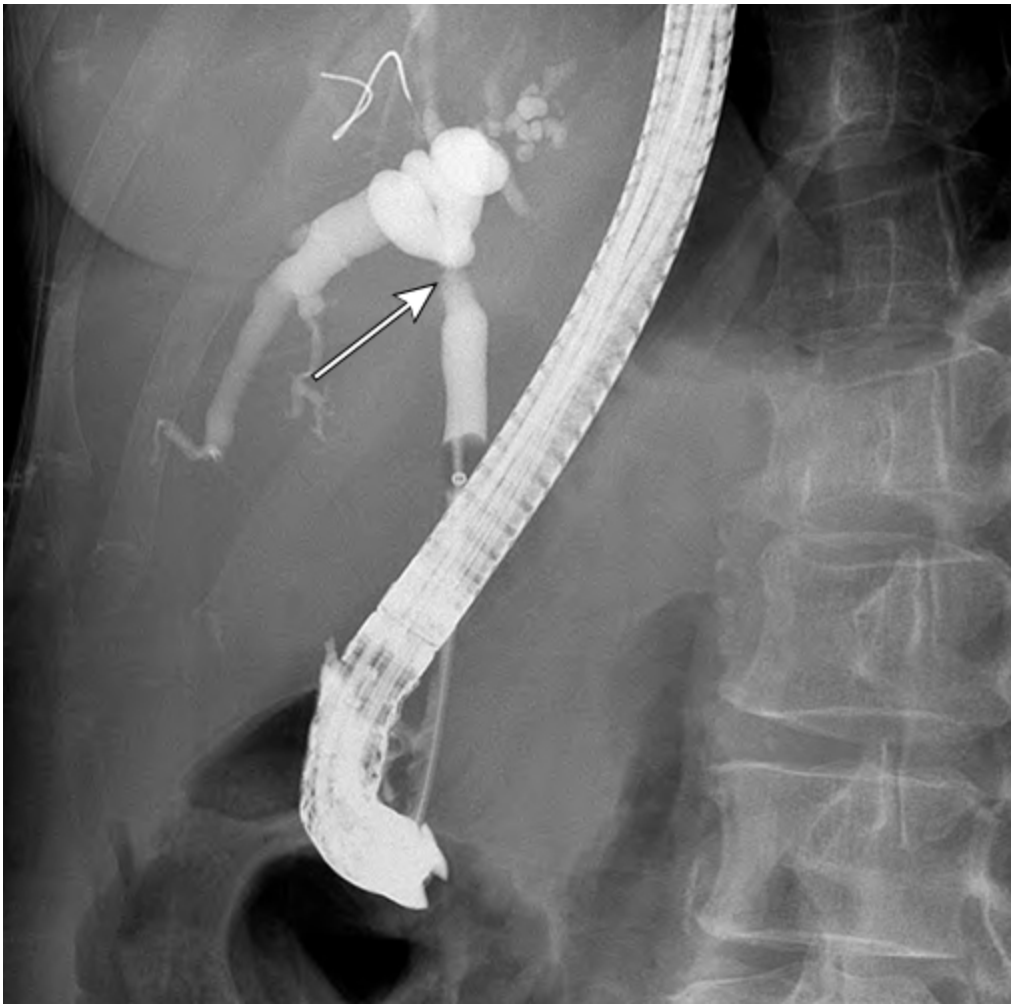


Normal intraductal ultrasound demonstrating the common hepatic duct (CHD), cystic duct, portal vein (PV), and hepatic artery (HA).

Courtesy of Drs. Micheal J Levy, Enrique Vazquez-Sequeiros, and Maurits J Wiersema.

Graphic 74347 Version 4.0

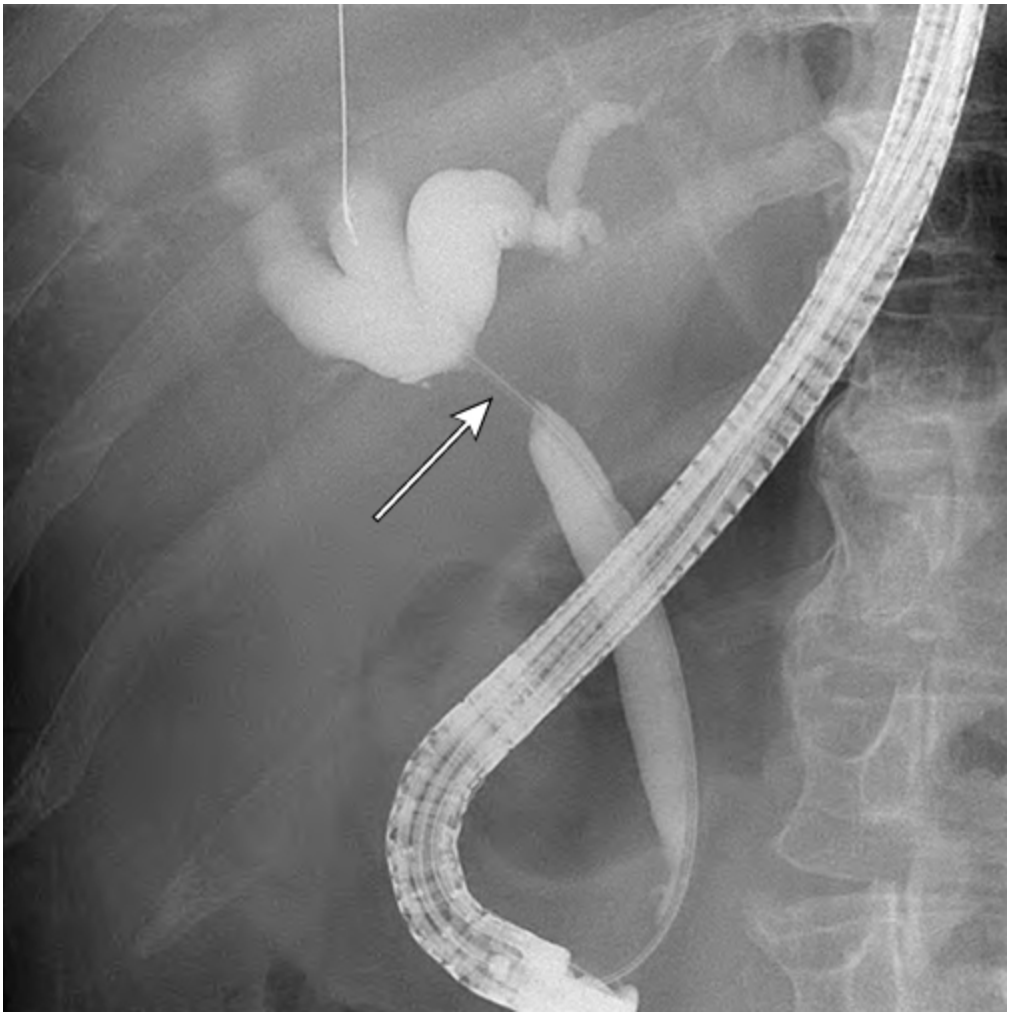
Common hepatic duct stricture



Cholangiogram showing a stricture of the common hepatic duct and hepatic duct bifurcation.

Graphic 78679 Version 2.0

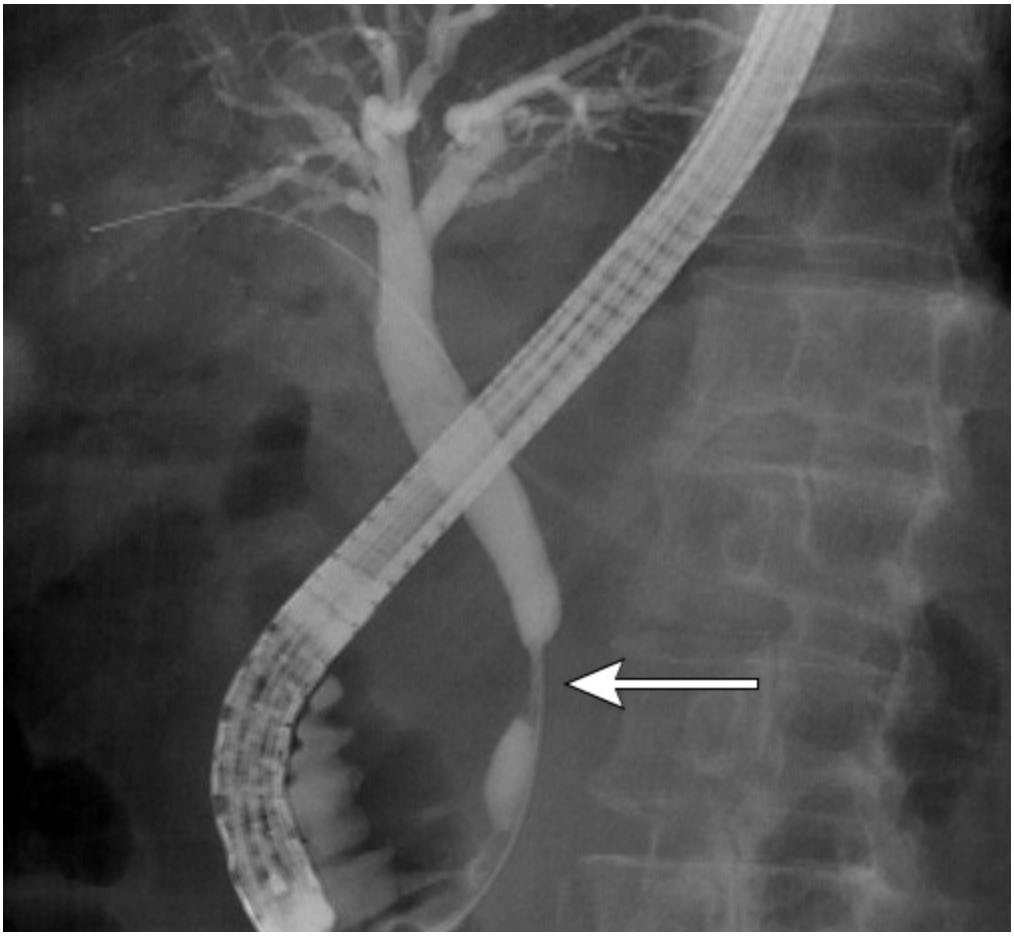
Stricture at the hepatic duct bifurcation



Cholangiogram showing a stricture at the hepatic duct bifurcation.

Graphic 61451 Version 2.0

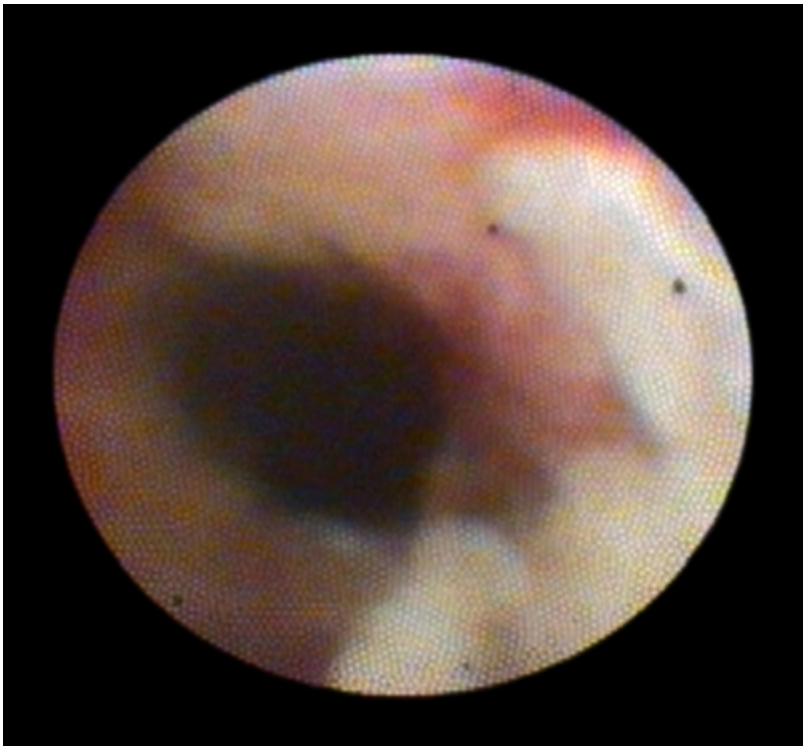
Distal common bile duct stricture



Cholangiogram showing a stricture in the distal common bile duct.

Graphic 79883 Version 2.0

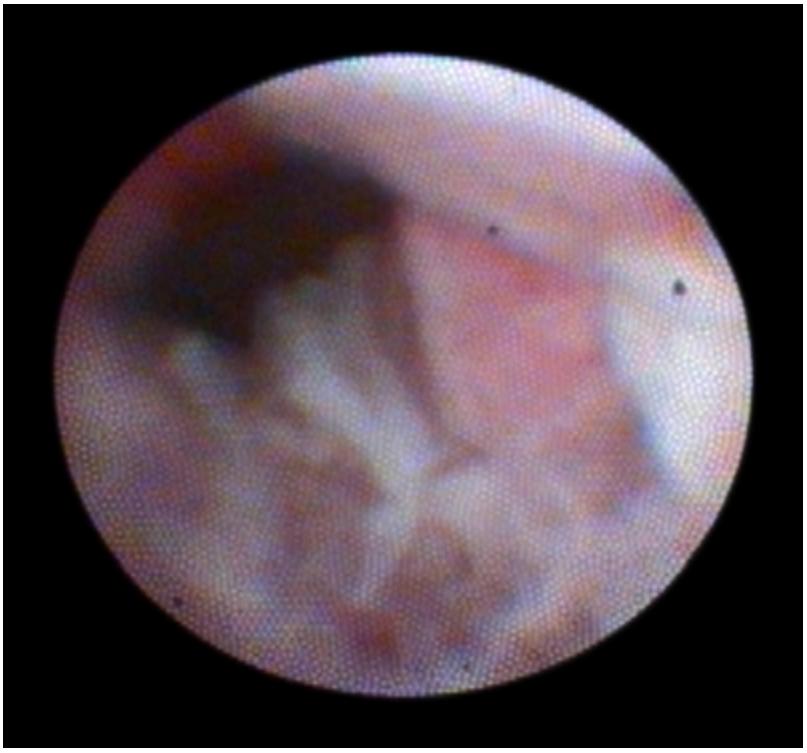
Ulcerated stricture on cholangioscopy



Catheter-based cholangioscopy showing an ulcerated bile duct stricture.

Graphic 50986 Version 2.0

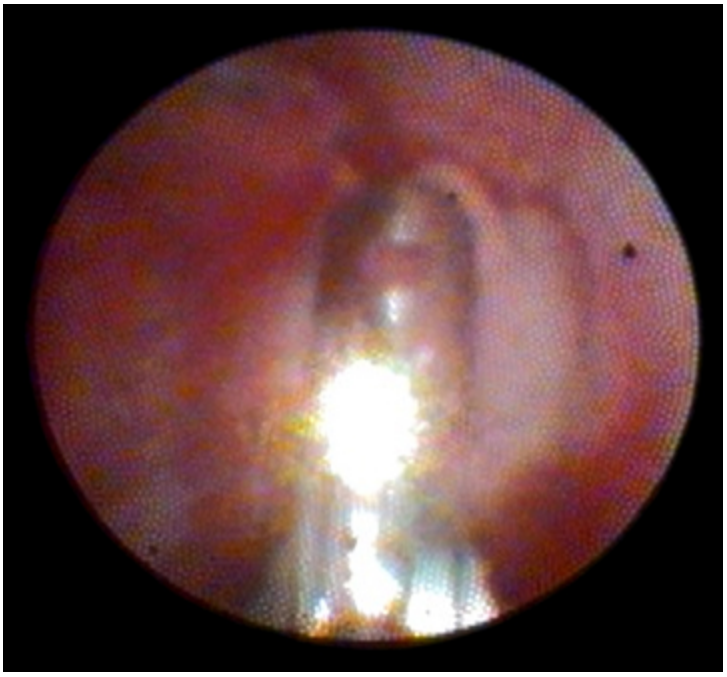
Cholangiocarcinoma on cholangioscopy



Fiberoptic cholangioscopy showing a nodular, ulcerated stricture in the bile duct.

Graphic 61611 Version 2.0

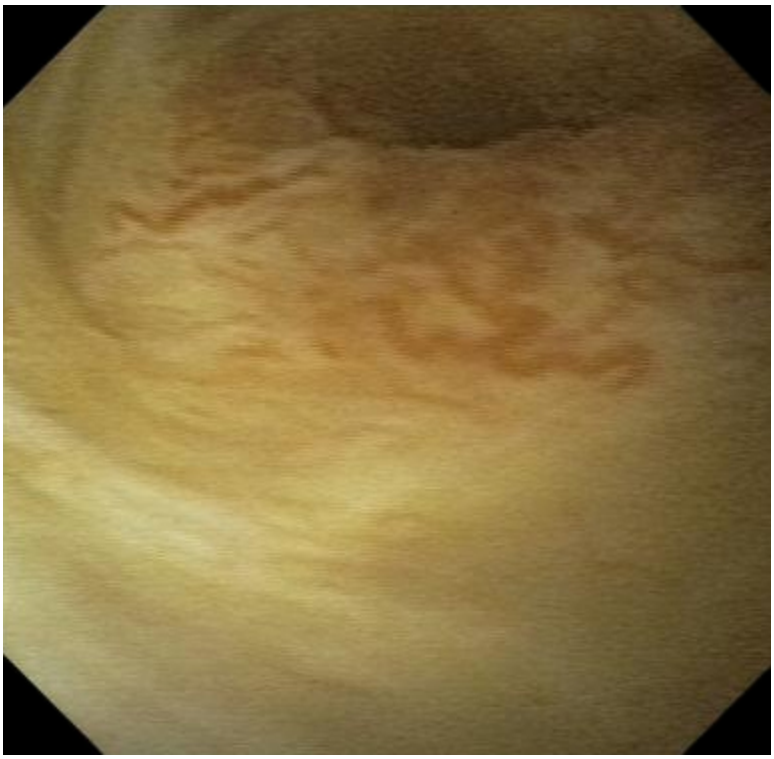
Cholangioscopy-directed biopsy of a stricture



Fiberoptic cholangioscopy showing biopsy forceps obtaining a tissue sample from an ulcerated stricture due to cholangiocarcinoma.

Graphic 68712 Version 2.0

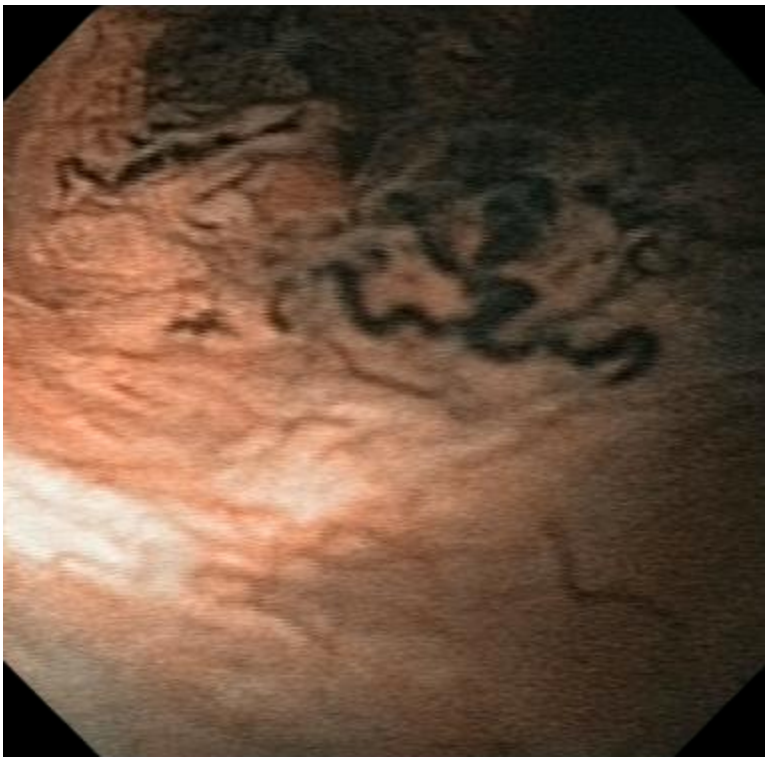
White light imaging of tumor vessels in cholangiocarcinoma



Cholangioscopy showing tumor vessels in a patient with cholangiocarcinoma.

Graphic 73222 Version 2.0

Narrow band imaging of tumor vessels in cholangiocarcinoma



Video cholangioscopy using narrow band imaging showing tumor vessels in a patient with cholangiocarcinoma.

Graphic 55989 Version 5.0

Contributor Disclosures

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