Cholangiocarcinoma: Introduction

The terms cholangiocarcinoma and bile duct cancer are often used interchangeably. Primary biliary tract malignancies affect one in every 100,000 people per year in the United States. More than 95% of these malignancies are cholangiocarcinomas (epithelial adenocarcinomas) frequently found in the extrahepatic biliary tree. This form of cancer is slightly more prevalent in males than females (1.3:1.0) and usually affects patients in the fifth to seventh decade of life.

What is Cholangiocarcinoma?

Cholangiocarcinoma is a primary malignant tumor originating from cells that resemble biliary epithelium. The gross appearance is that of one or more firm, white masses (Figure 2).

The tumor(s) is usually small and may arise anywhere along the biliary tree, from the small intrahepatic bile ducts to the common bile duct. Microscopically, cholangiocarcinoma may resemble adenocarcinoma. These bile ductule tumors may be well differentiated, while others are poorly differentiated (Figure 3).
Cholangiocarcinomas are usually slow-growing tumors that spread locally via the lymphatic system. Treatment and long-term prognosis are dependent upon the location of the mass. Lesions located in the distal or middle portion of the extrahepatic bile duct (20% and 35%, respectively) have a better prognosis than tumors in the proximal third, which include about 45% of bile duct cancers (including Klatskin’s tumors — hilar variants).

Large solitary tumors are characteristic of peripheral cholangiocarcinoma; however, a multinodular type may occur. These tumors have a fibrous stroma, are firm and grayish white in color, and are not well vascularized. Hilar cholangiocarcinoma are usually firm, intramural, annular tumors that encircle the bile duct, or may be bulky hard masses that are on the duct or hilar region and extend into the liver. They may also appear as a spongy friable mass in the lumen of the bile duct. There may be metastatic nodules throughout the liver with dilation of bile ducts peripheral to the mass.

**Symptoms**

The clinical presentation of cholangiocarcinoma depends on the anatomic location of the tumor(s). Patients with hilar cholangiocarcinoma, (tumor located in the area of confluence of right and left hepatic ducts) most commonly present with jaundice, pruritis, abdominal pain, fever, weight loss and/or progressive weakness (Figure 4). Patients with peripheral cholangiocarcinoma (tumor originating from small intrahepatic ducts) may present only with vague abdominal pain, unexplained weight loss, weakness and worsening fatigue. Jaundice and pruritus may not be apparent until very late in the disease course, when there is occlusion of segmental bile ducts. Patients with distal cholangiocarcinoma (tumors involving extrahepatic bile ducts) usually have early onset of jaundice and pruritus without abdominal pain. Upon physical examination, these patients usually have a palpable distended gallbladder (Courvoisier’s sign).

Cholangiocarcinoma may occur in the setting of primary sclerosing cholangitis and may be difficult to diagnose. Clues that may suggest an underlying carcinoma include a stricture that is refractory to therapy, or sudden deterioration in biochemical tests of liver function.
Cholangiocarcinoma: Anatomy

Anatomy

The liver arises from the ventral mesogastrium, and only the upper posterior surface is outside of that structure. The ligamentum teres and falciform ligament connect the liver to the anterior body wall. The lesser omentum connects it to the stomach and the coronary and triangular ligaments to the diaphragm. The liver is smooth and featureless on the diaphragmatic surface and presents with a series of indentations on the visceral surface where it meets the right kidney, adrenal gland, inferior vena cava, hepatoduodenal ligament and stomach.

The liver can be considered in terms of blood supply, hepatocytes, Kupffer cells and biliary passages. The liver receives its blood supply from the portal vein and hepatic artery, the former providing about 75% of the total 1500 mL/min flow. Small branches from each vessel (the terminal portal venule and terminal hepatic arteriole) enter each acinus at the portal triad (Figure 6). Pooled blood then flows through sinusoids between plates and hepatocytes exchanging nutrients. The hepatic vein carries all efferent blood into the inferior vena cava, and a supply of lymphatic vessels drains the liver.

Liver cells, or hepatocytes, comprise the bulk of the organ, which carry out complex metabolic processes. Hepatocytes are responsible for the liver’s central role in metabolism. The functions of these cells include the formation and excretion of bile, regulation of carbohydrate homeostasis, lipid synthesis and secretion of plasma lipoproteins, control of cholesterol metabolism, formation of urea, serum albumin, clotting factors, enzymes and numerous proteins. The liver also aids in the metabolism and detoxification of drugs and other foreign substances.

Kupffer cells line the hepatic sinusoid and are part of the reticuloendothelial system filtering out minute foreign particles, bacteria and gut-derived toxins. They also play a role in immune processes involving the liver.

Biliary passages begin as tiny bile canaliculi formed by hepatocytes. These microvilli-lined structures progress into ductules, interlobular bile ducts and larger hepatic ducts. Outside the porta hepatis, the main hepatic duct joins the cystic duct from the gallbladder to form the common bile duct, which drains into the duodenum.

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Cholangiocarcinoma: Causes

**Primary Sclerosing Cholangitis**
There is a high incidence of cholangiocarcinoma in patients (Figure 7) with ulcerative colitis (1 in 256) and primary sclerosing cholangitis (4–20%). The cumulative risk for cholangiocarcinoma is 11.2% at 10 years after diagnosis.

![Figure 7](image)

**Liver Flukes**
Cholangiocarcinoma is more common in areas endemic to liver fluke infection (Hong Kong, Thailand). Liver flukes, such as Clonorchis sinensis or Opisthorchis viverrini, usually enter human's gastrointestinal tract after ingestion of raw fish. Parasites travel via the duodenum into the host’s intrahepatic or extrahepatic biliary ducts. Liver flukes cause bile stasis, inflammation, periductal fibrosis and hyperplasia, with the subsequent development of cholangiocarcinoma (Figure 8).

![Figure 8](image)

**Gallstones**
Gallstones vary in size, shape and number, and may be found throughout the biliary tract. The link between cholangiocarcinoma and gallstones is unclear. Intrahepatic gallstones may cause chronic obstruction to bile flow, promote micro injury of the bile ducts, and are associated with a 2–10% risk of the development of cholangiocarcinoma (Figure 9). Congenital cystic dilation of intrahepatic biliary ducts (Carol’s disease), and choledochus cysts have also been closely associated with development of cholangiocarcinoma.

![Figure 9](image)
Thorotrast
The radiocontrast agent, Thorotrast, was in use from the late 1920s through the 1950s. There are many reports of development of cholangiocarcinoma 30–35 years after exposure to this contrast material.
Cholangiocarcinoma: Diagnosis

Laboratory tests
Biochemical tests of liver function may reveal a cholestatic picture with elevated total bilirubin and alkaline phosphatase. This pattern is non-specific for cholangiocarcinoma and may be found with any cause of obstruction to bile flow. The levels of blood bilirubin and alkaline phosphatase usually correlate with degree and duration of obstruction of the biliary ducts. Fluctuation in the serum bilirubin level may reflect incomplete obstruction and involvement of one hepatic duct.

CEA and CA19-9
Carcinoembriogenic antigen (CEA) and CA 19-9 are blood tests for non-specific markers of underlying gastrointestinal malignancies. These tests are positive in more than 40% of patients with cholangiocarcinoma, but usually only in late stages of the tumor.

Alpha-Fetoprotein (AFP)
Alpha-fetoprotein is another blood test commonly used to identify markers of possible hepatobiliary malignancy. This test is usually elevated in patients with cholangiocarcinoma, but not to the degree of elevations in patients with hepatocellular carcinoma.

Radiological Diagnosis

Ultrasound
Transabdominal ultrasound is a totally painless, non-invasive procedure. The test does not require special preparation, although it is technically easier in patients with at least six hours of fasting. Transabdominal ultrasound is usually recommended as the first imaging modality for the investigation of patients with suspected cholangiocarcinoma. In hilar cholangiocarcinoma, ultrasound demonstrates bilateral dilation of intrahepatic ducts, and right and left hepatic ducts. In rare cases, the tumor itself can be visualized as either a hypoechoic (decreased echodensity) or hyperechoic (increased echodensity) rounded mass located just distal to dilated biliary ducts. Peripheral cholangiocarcinoma may be suspected if abdominal ultrasound demonstrates local dilation of intrahepatic ducts or isolated dilation of the biliary tree inside one lobe of the liver. In both peripheral and hilar cholangiocarcinoma, biliary ducts distal to the obstruction (common hepatic duct and common bile duct) are not dilated. In patients with hilar cholangiocarcinoma and complete obstruction of both right and left hepatic ducts, extrahepatic bile ducts and the gallbladder appear empty (collapsed) because there is no bile flow out of the liver. In patients with distal cholangiocarcinoma, ultrasound demonstrates dilated intra- and extrahepatic ducts along with significant dilation of the gallbladder. Peripherally located tumors cause segmental or lobular obstruction of the biliary tree. Bile flow from the rest of the liver is preserved. Extrahepatic bile ducts and the gallbladder appear normal (filled with bile) in patients with peripheral cholangiocarcinoma.

Transabdominal ultrasound can also detect the presence of liver metastases as single or multiple rounded lesions of different echogenicity.

Computed Tomography (CT)
Computed tomography may detect lesions of low-density mass associated with dilated biliary ducts (Figures 10 and 11). Similar to transabdominal ultrasound, computed tomography produces different pictures depending on location of the tumor and the level and degree of obstruction. Hilar masses cause bilateral dilation of intrahepatic bile ducts. Distal tumors produce universal dilation of intra- and extrahepatic bile ducts and gallbladder. Peripheral cholangiocarcinoma may present with atrophy, decreased size of the affected lobe of the liver with minimal dilation of the small intrahepatic ducts. In contrast to hypervascular hepatocellular carcinomas, cholangiocarcinomas are usually hypovascular and appear hypodense or isodense compared to liver parenchyma. Computed tomography is also capable of demonstrating the presence of liver metastases or lymphatic nodules and tumor growth into surrounding organs.

Magnetic Resonance Imaging (MRI)
Magnetic resonance imaging is slightly superior to computed tomography in visualization of tumors. The recent addition of magnetic resonance cholangiography (MRCP) allows visualization of both dilated biliary ducts proximal to the tumor and normal-sized extrahepatic ducts distal to the level of occlusion. Magnetic resonance cholangiography (MRCP) images obtained from the newest diagnostic equipment are comparable in quality to those obtained with Endoscopic Retrograde Cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography. Ductal or intravenous injection of contrast medium is not necessary and the patient is not exposed to irradiation. The MRCP creates an enhanced MRI and may be adjusted to optimally visualize the biliary and pancreatic ducts.
Endoscopic Diagnosis
Gastrointestinal endoscopy allows the physician to visualize and biopsy the mucosa of the upper gastrointestinal tract. Endoscopy permits visualization of the esophagus, stomach and duodenum. The enteroscope allows visualization of at least 50% of the small intestine, including most of the jejunum and different degrees of the ileum. During this procedure, the patient may be administered a pharyngeal topical anesthetic agent that helps to prevent gagging. Pain medication and a sedative may also be administered prior to the procedure. The patient is placed in the supine position on his/her left side (Figure 12).

Endoscopic Retrograde Cholangiopancreatography (ERCP)
Endoscopic retrograde cholangiopancreatography is an endoscopic procedure that involves the use of fiberoptic endoscopes (Figure 13). The side-viewing endoscope is introduced into the second portion of duodenum, and contrast material is injected into the bile ducts via major duodenal papilla under fluoroscopic guidance (Figure 14). Multiple x-ray pictures are taken to visualize the distribution of the contrast in the biliary tree. Endoscopic retrograde cholangiopancreatography can demonstrate normal diameter and structure of the extrahepatic ducts distal to occlusion and dilated intrahepatic ducts proximal to occlusion (Figure 15).
Cholangiocarcinoma on ERCP will produce a filling defect or area of narrowing, with irregular borders at the level of occlusion (Figure 16). Spontaneous bleeding from the tumor may cause longitudinal filling defects on ERCP. These blood clots, if not removed, can be misleading in terms of demonstrating the true size and extent of the tumor into the lumen of bile ducts. Samples of tissue from the tumor can be obtained during the procedure by brush or biopsy under fluoroscopic guidance to confirm the diagnosis (Figure 17). ERCP can usually demonstrate the distal level of occlusion. In cases of complete occlusion, ERCP may not be able to evaluate condition of the biliary tree proximal to the tumor. This group of patients would benefit from percutaneous transhepatic cholangiography.

Endoscopic Ultrasound (EUS)

Endoscopic ultrasound is a combination of endoscopy with ultrasound to obtain images within the gastrointestinal tract. The procedure is performed after the patient has been prepared (the same as for standard upper endoscopy). Topical anesthesia and intravenous sedation are administered and the scope is passed through the mouth and into the stomach. The endoscope is then directed to the area of clinical interest. Endoscopic ultrasound has been used for the diagnosis of carcinomas of the bile duct.

Because the common bile duct and gallbladder are in close proximity to the duodenum and distal stomach, EUS has proven to be a useful tool for imaging these organs (Figure 18). This technique has been used to stage carcinomas of the bile duct and the gallbladder.
Percutaneous Radiological Diagnosis

Percutaneous Transhepatic Cholangiography

Percutaneous transhepatic cholangiography is an invasive procedure performed by a radiologist under fluoroscopic guidance. A small needle is introduced through the liver into one of the peripheral biliary ducts. Contrast material is injected through the needle and x-ray pictures obtained to document the biliary tree anatomy. In patients with cholangiocarcinoma, percutaneous transhepatic cholangiogram findings are similar to those obtained by ERCP (dilated intrahepatic ducts, normal size extrahepatic ducts, irregular filling defects and strictures at the level of occlusion). If cholangiocarcinoma causes complete obstruction of the biliary tree, percutaneous transhepatic cholangiography is the ideal method to visualize the ducts proximal to obstruction. Bile ducts distal to obstruction may not be visible on percutaneous transhepatic cholangiography in this situation (Figure 19).

Angiography

Angiography may be used for pre-operative staging. It is used to evaluate the level of biliary obstruction and to assess resectability and invasion of the portal vein and/or hepatic artery. This procedure detects vascular encasement (seen as gradual narrowing of the vessel with irregular borders), venous obstruction (complete obliteration of the lumen), and also aids in the delineation of anatomy, prior to surgical resection. Angiography is an accurate means of diagnosing mesenteric vascular disease, portal hypertension and gastrointestinal hemorrhage.

Patients are given mild sedatives and an analgesic prior to angiography. During the procedure, blood pressure, electrocardiogram, oxygen saturation and pedal pulses are monitored. There may be some slight discomfort at the puncture site, as well as a burning sensation during contrast injection. The procedure can be safely performed on an outpatient basis. After four hours of observation, patients are ambulated and discharged (often with an attendant).
Surgical Therapy
Surgical excision of biliary tract tumors is the treatment of choice in cholangiocarcinoma as it is the only therapeutic option that offers the potential for cure. Surgical approaches have become increasingly aggressive over the last decade since it has become apparent that curative treatment is dependent upon aggressive excision. This often involves a major liver resection. The objective is complete removal of the tumor and biliary drainage. Operative mortality in the hands of an experienced surgeon is extremely low (close to 0% for local resections and less than 10% for procedures with hepatic resection). Surgical management provides improved survival rates and quality of life.

Surgical treatment is dependent upon the localization of the mass. Treatment of hilar cholangiocarcinoma requires resection of the bifurcation of common hepatic duct. The procedure starts with exploration of the peritoneal cavity to detect possible dissemination and resectability of the tumor. If the cholangiocarcinoma appears resectable, the gallbladder should be mobilized and the distal common bile duct divided. Careful dissection continues proximally until right and left hepatic ducts are separated above the tumor. Biliary reconstruction is achieved through bilateral hepatojejunostomy on a Roux-en-Y intestinal loop above the transhepatic silicone biliary stents. If cholangiocarcinoma extensively involves one lobe of the liver and relatively spares the other lobe, resection of the affected lobe or caudate lobe may be warranted with subsequent unilateral (in case of resection of right or left hepatic lobectomy) or bilateral (in case of caudate lobe resection) hepatojejunostomy (see Figures 21 and 22).

Surgical treatment of peripheral cholangiocarcinoma is similar to hepatocellular carcinoma and requires hepatic lobectomy or segmentectomy depending upon the size of the tumor. Dissection of the hepatic ducts confluence and reconstructive hepatojejunostomy is not necessary after resection of peripheral cholangiocarcinoma.

Surgical treatment of distal cholangiocarcinoma can be divided into three groups. For tumors of the proximal third of extrahepatic ducts, surgery usually includes resection of the tumor with subsequent hepatojejunostomy (Figure 21 and 22).

For tumors of the middle third of extrahepatic duct, surgical options include resection of the mass with possible primary end-to-end bile duct anastomosis (for early small tumors) or hepatojejunostomy (if large portion of extrahepatic ducts should be removed).

For tumors located in distal common bile duct, the Whipple procedure is recommended (same as for ampullary tumors).
Surgery remains the primary treatment of cholangiocarcinoma, even for advanced stages of the tumor. Resectability of the tumor and survival rates in patients with cholangiocarcinoma depend on location of the tumor and spread of the disease at the time of presentation. Survival rates are higher in specialized institutions where a multidisciplinary team, including surgeon, oncologist, endoscopist, interventional radiologist and supporting staff are involved. Reported resectability increased with the more distal location of the tumor (50% for peripheral cholangiocarcinoma vs. 56% for hilar vs. 91% for distal tumors). Five-year survival rates for resected peripheral, hilar and distal cholangiocarcinoma were 44%, 11% and 28%, and median survival rates were 26, 19, and 22 months, respectively.

**Endoscopic Therapy**

Endoscopic biliary dilation may be used as a final palliative measure to relieve jaundice in patients who are poor surgical candidates, or as one of the steps prior to surgical intervention. This procedure requires use of a side-viewing endoscope to access the biliary duct and to introduce an inflatable balloon or series of endoscopic dilators over a guide wire. In many cases, a biliary sphincterotomy is performed prior to dilation and stent placement. After successful dilation, plastic or self-expanding metal stents (endoprostheses) may be placed into the biliary ducts. Plastic endoprostheses are smaller in diameter (ranging in size from 7.0–11.5 French) and are more prone to occlusion. Plastic stents should be replaced endoscopically at regular intervals (usually 8–12 weeks). In case of complete obstruction of biliary ducts, it may not be possible to advance an endoscopic guide-wire above the occlusion. In this situation, the percutaneous transfemoral approach may be preferable.

**Radiological Therapy**

Percutaneous transhepatic palliative biliary dilation is performed by an interventional radiologist and requires transcutaneous puncture of the peripheral bile ducts and the subsequent placement of 12–16 French polymeric catheters. In patients with hilar cholangiocarcinoma occluding both the right and left hepatic ducts, separate percutaneous tubes may be inserted into right and left biliary systems and advanced through the side of occlusion into the duodenum, if possible. These stents allow the drainage of bile into the duodenum. Percutaneous polymeric biliary stents are usually exchanged at regular intervals to prevent occlusion and infectious complications. Percutaneous self-expandable metallic stents are recommended as a definitive method of palliation in patients with cholangiocarcinoma who are not surgical candidates (Figure 28).
Other Therapeutic Approaches

Chemotherapy and Radiotherapy

Currently, no chemotherapeutic approach has been shown to positively affect the clinical outcome in patients with cholangiocarcinoma. In addition, external beam radiation has not demonstrated efficacy. Reports on long-term survivors after radiotherapy have shown that some individuals may benefit from treatment, but potential complications are significant (duodenitis, bile duct stenosis, duodenal stenosis). Encouraging results have been demonstrated using interstitial or intraoperative radiation. Internal radiation or brachytherapy may be useful as adjuvant therapy following surgery or as a palliative therapy in combination with biliary enteric bypass. Further investigation is needed to fully assess the potential of such therapies.

In unresectable cholangiocarcinoma, the therapeutic strategy is to improve cholestasis by placing an endoprosthesis across the tumor, or by performing a biliary bypass. These procedures do not affect tumor growth, and it is unclear if they improve survival. However, improvement of cholestasis does improve symptoms such as fatigue, diarrhea, anorexia, pruritis, jaundice and sleep pattern, thus improving quality of life. Because early morbidity and 30-day mortality is significantly higher with surgical procedures than endoscopic/percutaneous drainage, such interventional techniques are preferable.

Independent of the type of stricture, technically successful endoprosthesis placement can be achieved in 84-96% of these patients. Successful drainage is achieved in 69-91% of Bismuth type I and II stenosis, and 15-73% in Bismuth type III and IV tumors, with an associated mean survival of approximately 150 days and 65 days in each group, respectively. Insertion of permanent metal endoprosthesis improves occlusion rates and reduces the number of therapeutic interventions; however, does not lessen median survival time.

Chemotherapy and radiotherapy (external-beam radiotherapy and 192I brachytherapy) have been used to decrease tumor growth rates, however, no randomized prospective trial evaluating the effects of these therapies has been conducted. A retrospective study comparing palliative endoscopic stenting versus stenting combined with radiotherapy showed no significant difference in median survival time. Studies with chemotherapy are not interpretable because they include different liver malignancies and therapeutic regimens. The question remains whether additional radiotherapy or chemotherapy is of benefit to patients with unresectable cholangiocarcinoma.

Photodynamic Therapy (PDT)

Photodynamic therapy (PDT) is a new therapy that selectively destroys tumor tissue. A photosensitizer is administered and selectively retained by the target tumor tissue. The photosensitizer is nontoxic in its native state, however, after activation by a light at a particular wavelength, the photosensitizer becomes cytotoxic and produces local tissue destruction. The only relevant side effect seen to date is phototoxicity, which lasts often for 4-6 weeks after drug administration.

Animal and human pilot studies have shown a reduction of up to 60% of tumor volume after administration of PDT with hematoporphyrin. One trial using biliary PDT in patients with unresectable cholangiocarcinoma (Bismuth types III and IV tumors), who failed endoprostheses placement, has resulted in significant improvements in serum bilirubin levels and quality of life scores, with a 30-day mortality of 0% and median survival time of 439 days. Other trials investigating the effect of PDT in patients with unresectable hilar carcinoma who were treated with endoprostheses placement showed a six-month survival rate of 91%. Ninety-six percent of patients improved in terms of cholestasis, performance and quality of life. No adverse side effects were reported.

PDT appears to be a promising therapeutic approach for unresectable cholangiocarcinoma, and combines the two aims of treating cholestasis and reducing tumor growth. The apparent benefit in survival time, however, needs to be confirmed with randomized, controlled trials.