

Primary Sclerosing Cholangitis: Introduction

Primary sclerosing cholangitis (PSC) is a chronic, usually progressive, stricturing disease of the biliary tree. Remissions and relapses characterize the disease course. Primary sclerosing cholangitis may remain quiescent for long periods of time in some patients; in most cases, however, it is progressive.

The prevalence of primary sclerosing cholangitis in the United States is approximately 1–6 cases per 100,000 population. Most patients with primary sclerosing cholangitis are men (75%) with an average age of approximately 40 years at diagnosis. The overwhelming majority of patients affected with primary sclerosing cholangitis are Caucasian. The etiology is unknown but current opinion favors an immune cause. Management of this disease in the early stages involves the use of drugs to prevent disease progression. Endoscopic and surgical approaches are reserved for the time when symptoms develop. Liver transplantation may ultimately be required and offers the only chance for a complete cure. Patients with primary sclerosing cholangitis are at an increased risk for cholangiocarcinoma (10–15%).

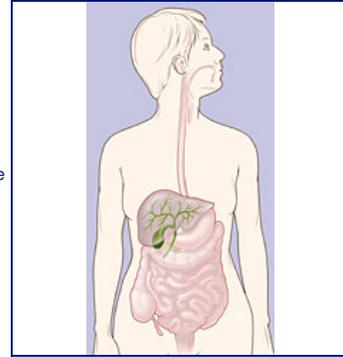


Figure 1. Location of the biliary tree in the body.

What is PSC?

Primary sclerosing cholangitis is a chronic fibrosing inflammatory process that results in the obliteration of the biliary tree and biliary cirrhosis. There is variability in the extent of involvement of the biliary system. The majority of patients with primary sclerosing cholangitis have underlying inflammatory bowel disease, namely ulcerative colitis or Crohn's disease. Patients with primary sclerosing cholangitis are more likely to have ulcerative colitis than Crohn's disease (85% versus 15%), with approximately 2.5–7.5% of all ulcerative colitis patients having primary sclerosing cholangitis. The strictures are located in both the intrahepatic and extrahepatic ducts in more than 80% of the patients, but about 10% of these patients have intrahepatic strictures only while less than 5% will have only extrahepatic strictures (Figure 2).

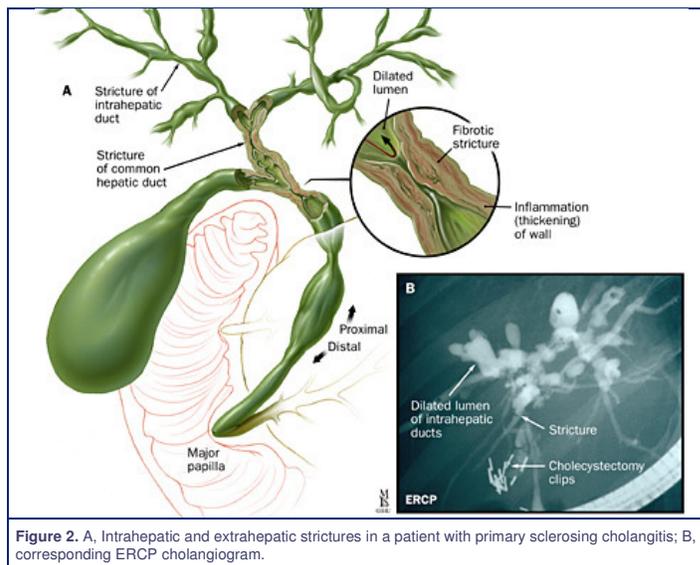


Figure 2. A, Intrahepatic and extrahepatic strictures in a patient with primary sclerosing cholangitis; B, corresponding ERCP cholangiogram.

Symptoms

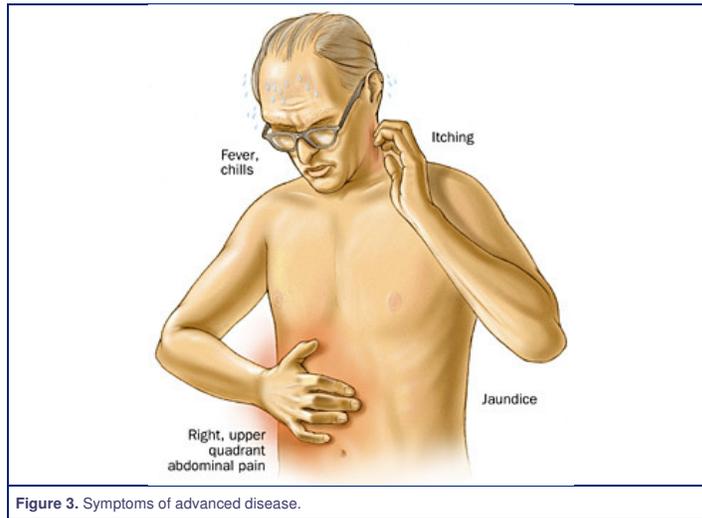


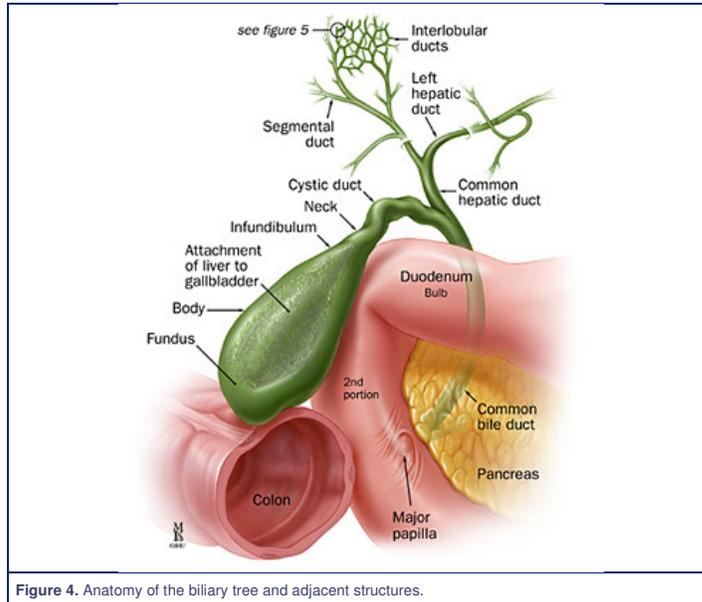
Figure 3. Symptoms of advanced disease.

Most patients with primary sclerosing cholangitis have no symptoms. These patients are usually diagnosed by the detection of abnormal biochemical tests of liver function on routine blood testing. Patients may remain asymptomatic for many years despite the presence of advanced disease.

When symptoms develop they are a result of obstruction to bile flow and include jaundice, itching, right upper quadrant abdominal pain, fever, and chills. Symptoms may also include weight loss and fatigue. The development of symptoms usually suggests the presence of advanced disease (Figure 3).

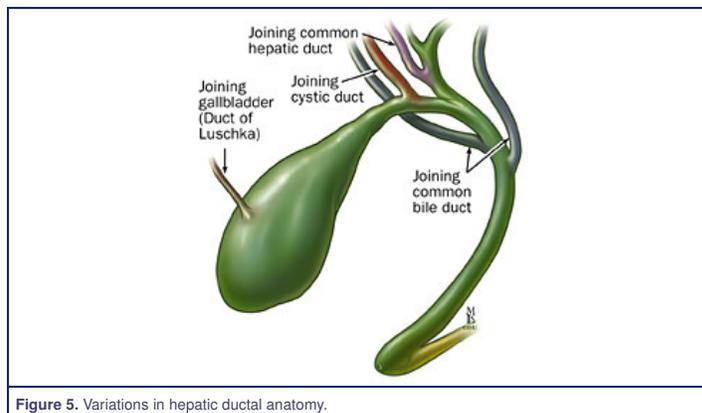
Primary Sclerosing Cholangitis: Anatomy

The gallbladder is located under the surface of the liver bound by vessels, connective tissue, and lymphatics. It has four regions: the fundus, body, infundibulum and the neck. The gallbladder terminates in the cystic duct and then enters the extrahepatic biliary tree. The fundus is the round, blind edge of the organ. It is comprised of fibrous tissue and projects just beyond the right lobe of the liver. The fundus leads to the body of the gallbladder, the largest part. The superior surface of the body is attached to the visceral surface of the liver, unless a mesentery is present. As a result, this allows for the direct spread of inflammation, infection or neoplasia into the liver parenchyma. The infundibulum is the tapering area of the gallbladder between the body and neck. This portion and the free surface of the body of the gallbladder lies close to the first and second portions of the duodenum and is close to the hepatic flexure and the right third of the transverse colon. The infundibulum is attached to the right lateral surface of the second part of the duodenum by the cholecystoduodenal ligament. The neck of the gallbladder is 5–7 mm in diameter often forming an S-shaped curve. It is superior and to the left narrowing into a constriction at the junction with the cystic duct (Figure 4).



The right and left hepatic ducts unite in an extrahepatic position in most cases. Length of the hepatic lobar duct varies from 0.5–1.5 cm. Usually, a short extrahepatic right lobar duct joins a longer left duct at the base of the right branch of the portal vein at differing angles. The common hepatic duct is formed by the merger of right and left hepatic ducts. In a minority of cases, a right segmental duct joining a left hepatic duct forms a third duct. There may be numerous variations in the left ductal system.

Twenty percent of the population has accessory hepatic ducts (Figure 5). In these individuals, the aberrant duct joins the common hepatic duct at various locations along its course. In rare instances this aberrant duct may join the cystic duct or a duct in the opposite lobe. Usually, however, these aberrant ducts are on the right side (Figure 5).



The hepatocyte-cholangiocyte level is the beginning of the biliary drainage system and is where portions of the hepatocyte membrane form the canaliculi (small channels). Bile drains from this level into intrahepatic ducts. The canaliculi and proximal ductal system converge in the canal of Hering. Smaller ducts combine to form the segmental bile duct. Segmental ducts within the liver form the right and left hepatic ducts. Union of ducts from hepatic segments II, III, and IV form the left lobar duct. The right hepatic duct drains segments V, VI, VII, and VIII.

Lining the intrahepatic ducts are cholangiocytes (epithelial cells). The cholangiocytes form complex networks of interconnecting tubes that are involved in secretory and absorptive processes. Cholangiocytes may be cuboidal in smaller ductal structures and columnar in larger structures and contain microvilli, which increase their surface area. These cells are believed to play a role in transport functions (protein from lymph or plasma into the bile). It is also probable that they are involved in the transport and the metabolism of bile acids. It is likely these cells are hormone-responsive (Figure 6).

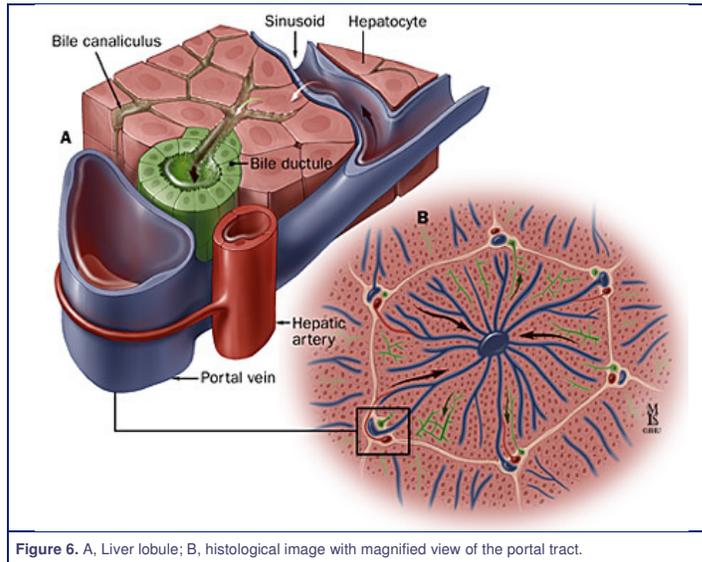


Figure 6. A, Liver lobule; B, histological image with magnified view of the portal tract.

The hepatic artery arises from the celiac axis and courses through the upper portion of the pancreas toward the liver. The hepatic artery gives rise to the gastroduodenal artery posterior and superior to the duodenum. It divides to right and left branches and then into smaller branches. In many cases a third artery supplies portions of segment IV and the right lobe of the liver.

The right, middle and left hepatic veins drain most of the hepatic flow and empty into the inferior vena cava. Each has a short extrahepatic segment. The largest vein, the right hepatic drains the right lobe of the liver. The middle vein drains the medial segment of the left lobe and some of the anterior segment of the right. The middle hepatic vein joins the left hepatic vein with variability in the juncture site. The left hepatic vein drains the left lateral segment of the liver (Figure 7).

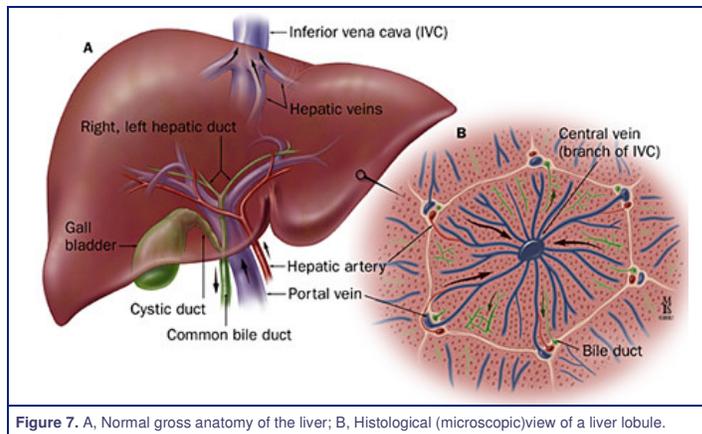


Figure 7. A, Normal gross anatomy of the liver; B, Histological (microscopic) view of a liver lobule.

Primary Sclerosing Cholangitis: Causes

Overview

The cause of primary sclerosing cholangitis is not known. However there are several theories as to why damage to the bile duct occurs. Genetic abnormalities of the immune regulation, viral infection, toxins from intestinal bacteria, bacteria in the portal venous system, ischemic vascular damage, and toxic bile acids from intestinal bacteria are all factors that have been implicated in the pathogenesis of primary sclerosing cholangitis.

Currently genetic and immunological factors are most favored to be responsible for the damage to the bile ducts. This is because there is a familial occurrence of this disease and an association with HLA-B8, DR3, DR2, and DR4. Evidence of abnormal immuno-regulation is evidenced by infiltration of the bile ducts with lymphocytes, increased serum gamma globulins, increased circulating immune complexes, and increased metabolism of complement C3 (Figure 8).

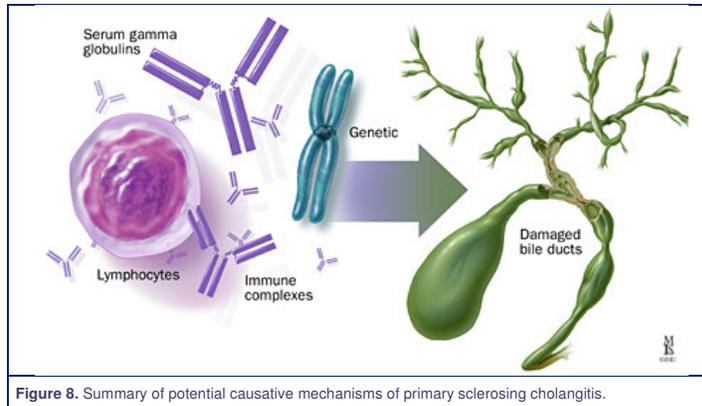


Figure 8. Summary of potential causative mechanisms of primary sclerosing cholangitis.

Primary Sclerosing Cholangitis: Diagnosis

Laboratory Tests

Biochemical tests of liver function are universally abnormal in patients with primary sclerosing cholangitis. Elevation of the serum alkaline phosphatase is the earliest abnormality detected. In more advanced disease a cholestatic pattern of abnormal biochemical tests of liver function is found with elevations of serum bilirubin and mild-to-moderate increases in serum aminotransferase levels. Elevation of the white cell count may suggest an underlying infection of bile namely acute cholangitis. Hypergammaglobulinemia (30%) and increased IGM levels (40%) are found. About two thirds of the patients with primary sclerosing cholangitis have perinuclear antineutrophilic cytoplasmic antibodies and HLA-DRw52a. In addition, copper metabolism is almost always abnormal as indicated by elevated urinary copper levels and serum caeruloplasmin values. Tests evaluating copper metabolism are prognostically significant.

Liver Biopsy

Liver biopsy is used for confirmation and staging of primary sclerosing cholangitis (Figure 9). The pathognomonic lesion, which is the onionskin lesion, is rarely seen. On liver biopsy there are four stages of primary sclerosing cholangitis that have been identified:

Stage 1

Infiltration of the bile duct by lymphocytes with degeneration of the epithelial cells of the bile duct. These findings are not present outside the portal triads.

Stage 2

There is more widespread involvement with fibrosis, inflammation infiltration in the periportal parenchyma with piecemeal necrosis of the periportal hepatocytes. The portal triads are enlarged but there is relative absence of bile ducts (bile ductopenia).

Stage 3

There are portal-to-portal fibrous bridges with severe degeneration of the ducts and ductopenia.

Stage 4

End stage liver disease with frank cirrhosis.

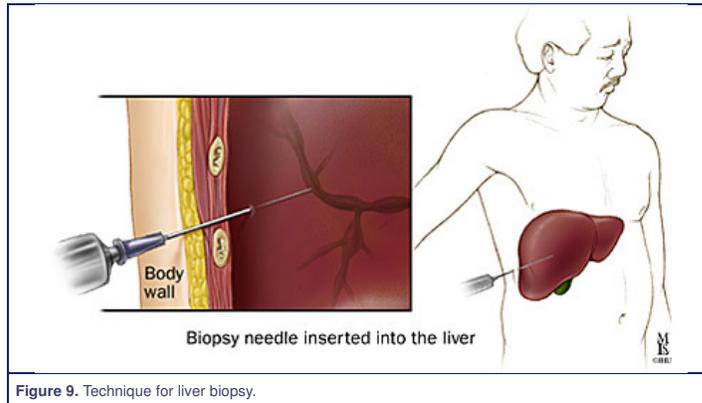


Figure 9. Technique for liver biopsy.

Endoscopic Diagnosis - ERCP

Endoscopic Retrograde Cholangiopancreatography (ERCP) is an endoscopic technique for visualization of the bile and pancreatic ducts. During this procedure the physician places a side-viewing endoscope in the duodenum facing the major papilla (Figure 11). The side viewing endoscope (duodenoscope) is specially designed to facilitate placement of endoscopic accessories into the bile and pancreatic ducts. The endoscopic accessories may be passed through the biopsy channel into the bile and pancreatic ducts (Figure 12). A catheter is used to inject dye into both pancreatic and biliary ducts to obtain x-ray images using fluoroscopy. During this procedure the physician is able to see two sets of images, the endoscopic image of the duodenum and major papilla, and the fluoroscopic image of the biliary and pancreatic ducts.

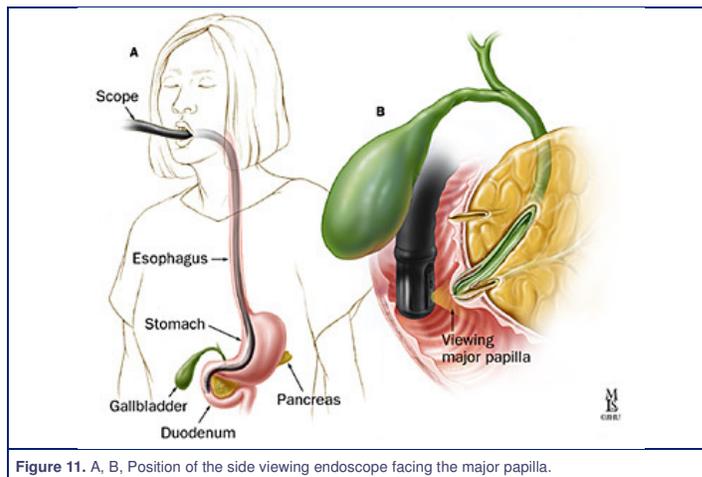


Figure 11. A, B, Position of the side viewing endoscope facing the major papilla.

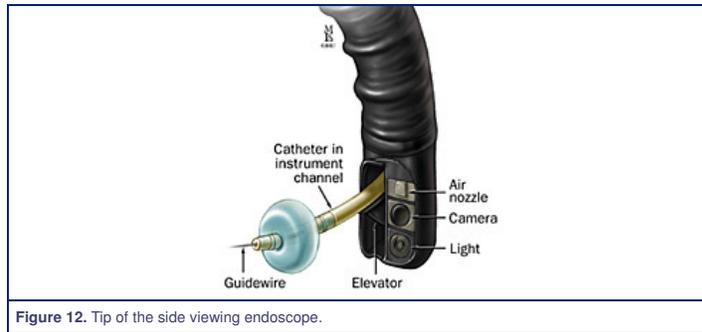


Figure 12. Tip of the side viewing endoscope.

The endoscope is designed to be held in the left hand with the thumb operating up and down angulation (Figure 13). The index finger operates the suction and air/water operations. The right hand is responsible for advancing, withdrawing and torquing the insertion tube. The right hand also operates left and right angulation of the scope as well as passing accessories through the instrument.

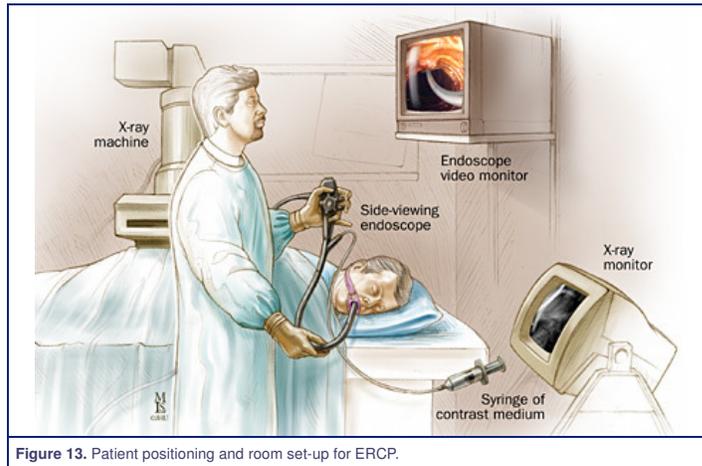


Figure 13. Patient positioning and room set-up for ERCP.

A variety of instruments can be utilized through the endoscope. Electrosurgical devices, such as snares, biopsy forceps, heater probes, BICAP devices for polyp removal and cauterization, dilation balloons, stents, catheters and esophageal prostheses may be employed. Lithotripsy devices, injection devices, brushes, forceps, scissors, and magnetic extraction devices may also be inserted through the scope (Figure 14). Cameras may be attached for photo documentation and dual examiner viewing. Video cameras and VCRs may also be attached for full-color motion picture viewing during endoscopic procedures or for later review.

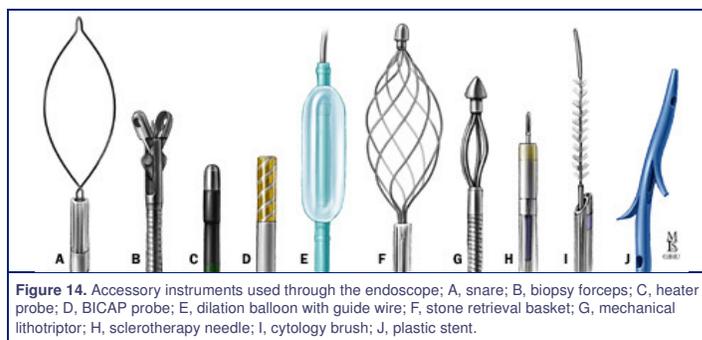


Figure 14. Accessory instruments used through the endoscope: A, snare; B, biopsy forceps; C, heater probe; D, BICAP probe; E, dilation balloon with guide wire; F, stone retrieval basket; G, mechanical lithotripter; H, sclerotherapy needle; I, cytology brush; J, plastic stent.

ERCP is the preferred method of visualization of the biliary tree. It is less invasive and easier to perform than percutaneous transhepatic cholangiography. The characteristic findings are that of multifocal areas of strictures and dilation, resulting in the characteristic "beaded" appearance of the duct. In most patients both intra and extrahepatic ducts are involved.

Percutaneous Transhepatic Cholangiography

Percutaneous transhepatic cholangiography should be considered as an alternative in patients in whom ERCP is unsuccessful. Patients with high-grade proximal biliary strictures may have poor visualization of the proximal biliary tree by ERCP and therefore require a percutaneous approach. The success of the percutaneous approach for visualization of the biliary tree is considerably less than for other causes of biliary obstruction (Figure 15).

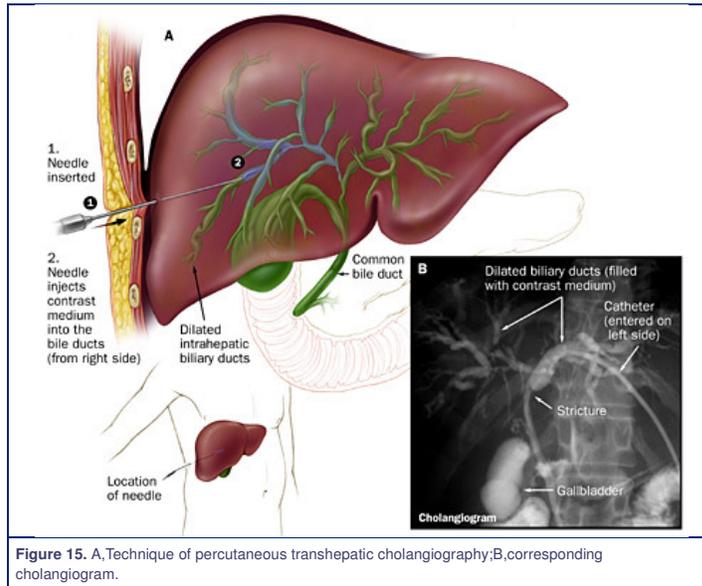


Figure 15. A, Technique of percutaneous transhepatic cholangiography; B, corresponding cholangiogram.

Magnetic Resonance Cholangiography

Magnetic Resonance Imaging (MRI) is becoming increasingly useful in the management of patients with primary sclerosing cholangitis. With recent refinements of the technique, excellent images of the bile ducts may be obtained in a non-invasive manner. Furthermore, information on the surrounding liver parenchyma such as the presence of a mass lesion suggestive of cholangiocarcinoma may be obtained.

Primary Sclerosing Cholangitis: Therapy

Medical Therapy

Ursodeoxycholic Acid

Ursodeoxycholic acid has been shown to improve the abnormal biochemical tests and liver histology but does not appear to affect survival or need for transplantation. Its mechanism of action is unknown but it increases the biliary secretion of bile acids and increases bile flow. Ursodeoxycholic acid prevents damage of liver cell membranes to toxic concentrations of chenodeoxycholic acid in in vitro studies.

Other Drug Therapy

Immunosuppressive and antiinflammatory agents have not been shown to improve the outcome of primary sclerosing cholangitis. These include the use of steroids and penicillamine.

Endoscopic Therapy

The goal of endoscopic therapy is dilation of strictures to a point that bile flow improves. This should result in an improvement in jaundice and decreased episodes of cholangitis. Traditionally, endoscopic therapy has been directed to patients with dominant strictures of the extrahepatic biliary tree. Unfortunately the presence of a dominant stricture occurs in only 10%–15% of patients with primary sclerosing cholangitis.

At the Johns Hopkins Hospital, we have utilized the technique of aggressive endoscopic therapy in patients with (or without) diffuse stricturing disease but without cirrhosis. The first step is endoscopic biliary sphincterotomy to facilitate passage of the balloon dilators (Figure 16).

Balloon dilatation of the total extra-hepatic ducts up to and including the common hepatic duct and hepatic bifurcation is then performed. Dilatation is performed from proximal to distal sequentially dilating the whole extrahepatic tree using high-pressure inflation balloons (up to 150psi) (Figure 17). Endoscopic stenting is used only if the strictures are refractory to therapy and is avoided because the low bile flow rate predisposes to early stent occlusion and cholangitis. Irrigation of the bile duct with steroids or saline has not been shown to be beneficial.

The main advantages of endoscopic therapy are that it is relatively non-invasive, can be repeated serially if necessary. Endoscopic therapy may decrease jaundice, pruritis and reduce the frequency of acute cholangitis. Although it does not alter the natural history or obviate the need for liver transplantation, endoscopic therapy may significantly improve the quality of life in patients awaiting transplantation.

Percutaneous Therapy

Interventional radiological techniques may be used in conjunction with an endoscopic or surgical approach. It may be useful in accessing the proximal biliary tree when a high-grade stricture precludes endoscopic visualization or when prior surgery makes endoscopic access difficult. Like the endoscopic approach, high-pressure balloon dilatation and stent placement may be performed. The disadvantage of the percutaneous approach is that it is more invasive than the endoscopic approach and requires an indwelling percutaneous catheter for varying lengths of time that may be uncomfortable to the patient (Figure 18).

Surgical Therapy

Non-transplant Surgery

Like the endoscopic approach, the goal of surgery is to improve bile flow, reduce jaundice and prevent further attacks of cholangitis. Non-transplant surgical approaches include resection of the extrahepatic bile ducts with biliary-enteric bypass with or without long-term biliary stenting. Another surgical approach is to resect the extrahepatic bile ducts including the bifurcation, dilate the intrahepatic ducts and then permanently stent the bile ducts with polymeric silicone transhepatic biliary stents (Figure 19).

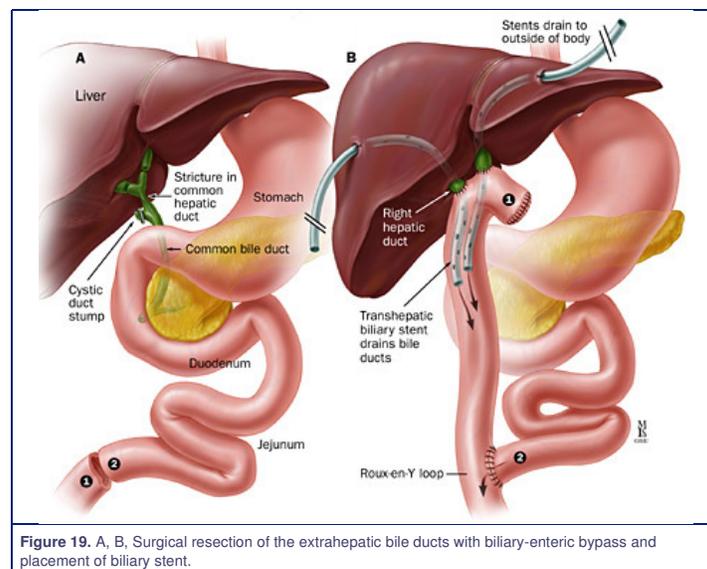


Figure 19. A, B, Surgical resection of the extrahepatic bile ducts with biliary-enteric bypass and placement of biliary stent.

In general these non-transplant surgical approaches may make liver transplantation technically more difficult and increase the morbidity and mortality of transplantation. However this approach may be useful in patients with high-grade strictures that are suspicious for cholangiocarcinoma.

Transplant Surgery

For more information about liver transplantation (Johns Hopkins Comprehensive Liver Transplantation Center)

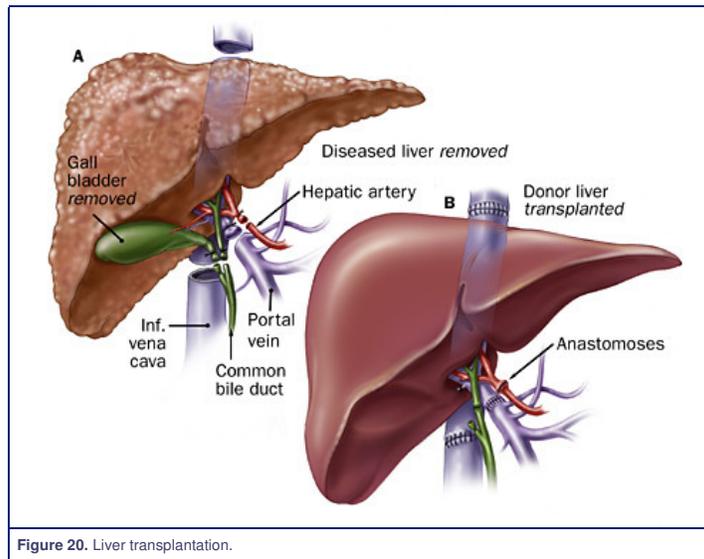


Figure 20. Liver transplantation.

Cholangiocarcinoma

For more information on Cholangiocarcinoma

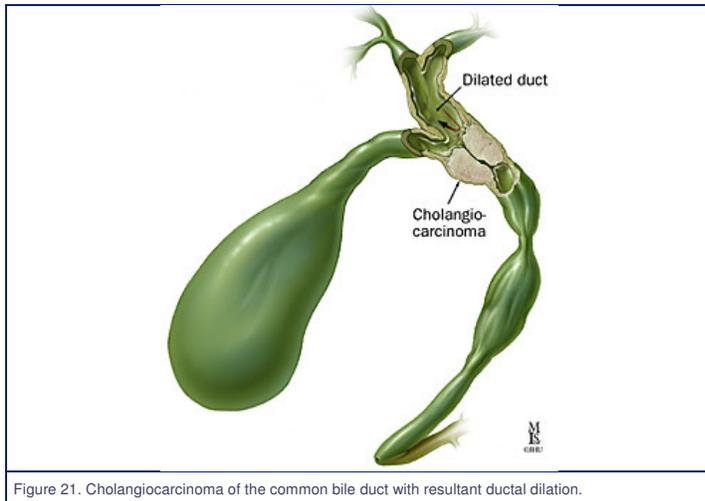


Figure 21. Cholangiocarcinoma of the common bile duct with resultant ductal dilation.

Cirrhosis

Cirrhosis, irrespective of its etiology, is a risk factor for the development of hepatocellular carcinoma. The risk is 3–4 times higher in patients with cirrhosis compared to those with chronic hepatitis in a given population. An increase in hepatocellular proliferation may lead to the activation of oncogenes and mutation of tumor suppressor genes. These changes, in turn, may initiate hepatocarcinogenesis. In low-incidence areas, more than 90% of patients with hepatocellular carcinoma have underlying cirrhosis. However, the presence of cirrhosis is less (approximately 80%) in high-incidence areas, which is probably related to vertical transmission of hepatitis B virus in these areas (Figure 22).

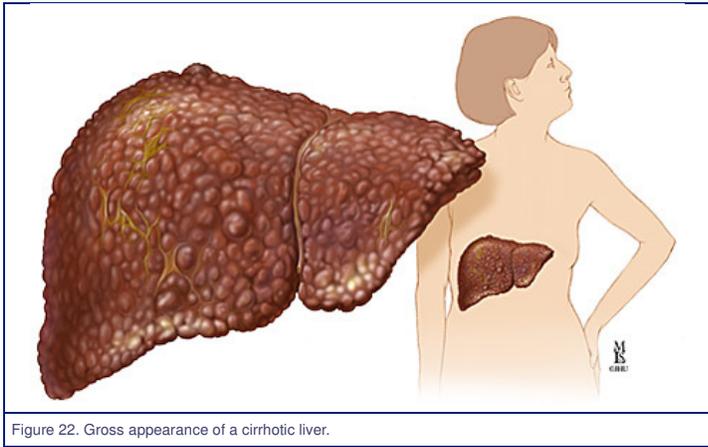


Figure 22. Gross appearance of a cirrhotic liver.

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