INTRODUCTION

Background

Bile duct stricture is an uncommon but challenging clinical condition that requires a coordinated multidisciplinary approach involving gastroenterologists, radiologists, and surgical specialists. Bile duct strictures may be asymptomatic but, if ignored, can cause life-threatening complications, such as ascending cholangitis, liver abscess, and secondary biliary cirrhosis.[1]

Unfortunately, most benign distal bile duct strictures are iatrogenic, resulting from operative trauma However, not all distal bile duct strictures are benign. Malignant biliary obstruction is commonly due to pancreatic carcinoma, cholangiocarcinoma and hepatic or nodal metastatic disease. Other causes include gall bladder carcinoma, hepatocellular carcinoma, lymphoma and advanced gastric or duodenal cancer. In these patients cancers of pancreas or biliary tree are diagnosed with advanced diseases. Only 20% of pancreatic cancers and 50% of cholangiocarcinomas are localized diseases potentially amenable to surgical resection.[2]

Drainage or stenting is to relieve biliary obstruction-related symptoms, prevent cholangitis. This optimizes the patient's condition for surgical resection or for receiving palliative chemotherapy or radiotherapy, bringing about an improvement in their quality of life, even if only for a matter of weeks or months Therefore, palliative care is of paramount importance.[3]

Epidemiology

Although quite uncommon, the exact prevalence of bile duct strictures is unknown. One major category of bile duct strictures is postoperative bile duct stricture, which usually occurs as a result of a technical mishap during cholecystectomy, causing bile duct injury. Data from many large series of patients in the United States have revealed that the incidence rate of major bile duct injury has risen with the advent of laparoscopic cholecystectomy from 0.1-0.2% for open to 0.2 to 0.7% for laparoscopic cholecystectomy.[4]

Gender

Data on the overall sex ratio of bile duct strictures are lacking. Some conditions causing bile duct strictures, such as PSC and chronic pancreatitis, are more common in men. The incidence of post-cholecystectomy strictures is comparable in men and women.[5]

Age

Data on the overall average age ratio of bile duct strictures are lacking. Some conditions causing bile duct strictures, such as PSC and chronic pancreatitis, are more common in third, fourth decades. While causes such as cholangiocarcinoma, cancer pancreas are more common in the fifth, sixth decades. The incidence of post-cholecystectomy strictures is highly variable.[6]

Mortality/Morbidity

Bile duct strictures, independent of etiology, can cause significant morbidity from recurrent obstructive jaundice, right upper quadrant abdominal pain, biliary stones, and recurrent episodes of ascending cholangitis.

The major determinant of mortality in patients with bile duct strictures is the underlying disease condition. Patients with biliary strictures due to operative injury, radiation, trauma, or chronic pancreatitis generally have a good prognosis. Conversely, patients with bile duct strictures due to PSC and malignancy have a less favorable outcome.[7]

Classification

Bile duct strictures can be classified according to the level of the obstruction in to distal and proximal with respect to the cystic duct, it can be classified into benign or malignant. Causes of biliary obstruction are summarized in table (1).[8]

Table I: Causes of biliary obstruction.

Proximal biliary obstruction		**Distal biliary obstruction**	
intrahepatic	**Portahepatis**	**suprapancreatic**	**intrapancreatic**
1-Primary sclerosing cholangitis 2-Space occupying liver lesion	1-Cholangiocarcinoma 2-PSC 3-Gall bladder carcinoma 4-HCC 5-Malignant lymph nodes 6-Liver metastases	1-pancreatic carcinoma 2-Cholangiocarcinoma 3-Postoperative injury 4-Metastatic diseases 5-Chronic pancreatitis 6-PSC	1-Pancreatic carcinoma 2-Pancreatitis 3-Choledocholithiasis 4-Ampullary stenosis /carcinoma 5-Duodenal carcinoma 6-Cholangiocarcinoma 7-PSC

Distal common bile duct strictures:

Etiology

Distal Bile duct strictures (biliary strictures) can be benign or malignant, described as follows: Benign biliary strictures are caused by a heterogeneous group of conditions that constitute only a small part of all strictures. The main manifestation of a stricture is scar contracture and stenosis of the duct, leading to cholestasis and eventually to secondary biliary cirrhosis. Despite the novel imaging modalities, the differential diagnosis between benign and malignant strictures remains challenging especially in cases without a mass lesion. A definitive diagnosis can be made in about half of the patients, and the rest are treated, as they are considered to have a malignant cause until proven otherwise.[9]

The most common causes of benign biliary strictures are as follows:[10]

1. Post-operative biliary tract injury.
2. Choleducolithiasis
3. Chronic pancreatitis.
4. Primary sclerosing cholangitis.
5. HIV cholangiopathy.
6. Choledochal cyst.
7. Recurrent pyogenic cholangitis.
8. Other causes includes (radiation, blunt abdominal trauma, systemic lupus, polyarteritis. nodosa, tuberculosis, histoplasmosis, etc).

I. Postoperative injury after biliary tract surgery

Benign biliary tract strictures can be the result of iatrogenic injury during surgery most commonly following cholecystectomy or may occur at site of biliary anastomosis, after hepatic resection or liver transplantation.[11]

Bile duct injuries are reported to be higher during laparoscopic cholecystectomy than open surgery, the estimated over all incidence of biliary injuries following laparoscopic cholecystectomy has been reported to be between 0.2%and 1.7%.[4]

Misidentification of anatomic structures during dissection especially in patients with anatomic variations of the biliary tree, presence of acute inflammation or fibrous adhesions in the gall bladder fossa, excessive use of electrocautry to control bleeding, inaccurate placement of clips, sutures, and ligations, and excessive traction on the gall bladder neck are major causes.[12]

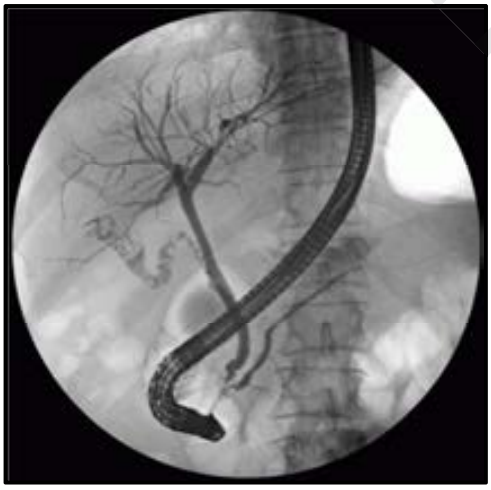

Figure (1): ERCP image showing the biliary tree and the main pancreatic duct and distal stricture. **(11)**

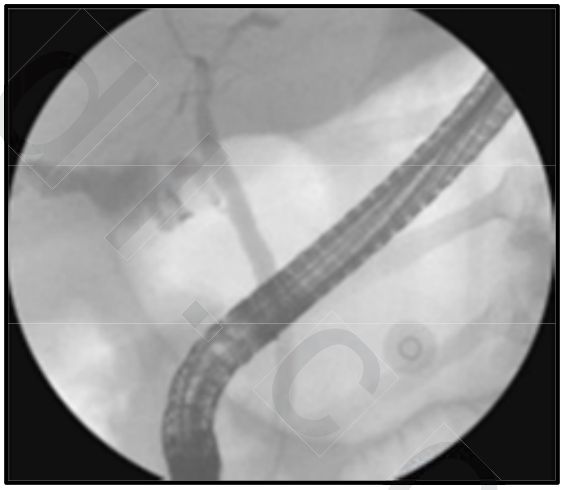

Figure (2): ERCP image of patient showing post cholecystectomy leak of contrast. **(11)**

Figure (3): ERCP image in a patient with common bile injury just below the confluence of the right and left hepatic ducts.[12]

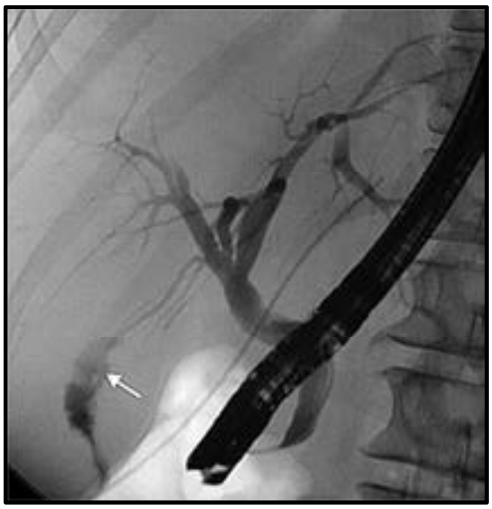

Figure (4): Bile duct leaks from an aberrant duct of Luschka.[12]

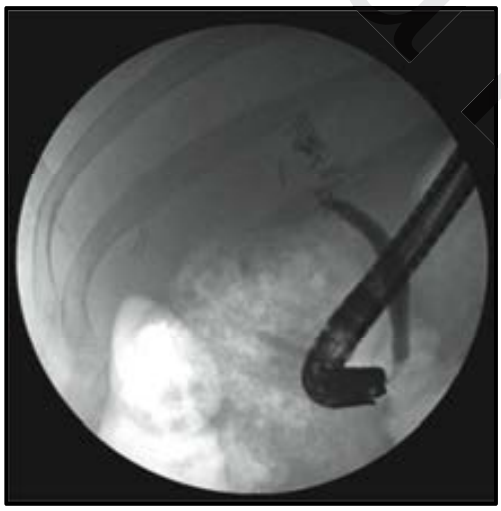

Figure (5): ERCP image of patient with postoperative biliary injury due to surgical clip.[12]

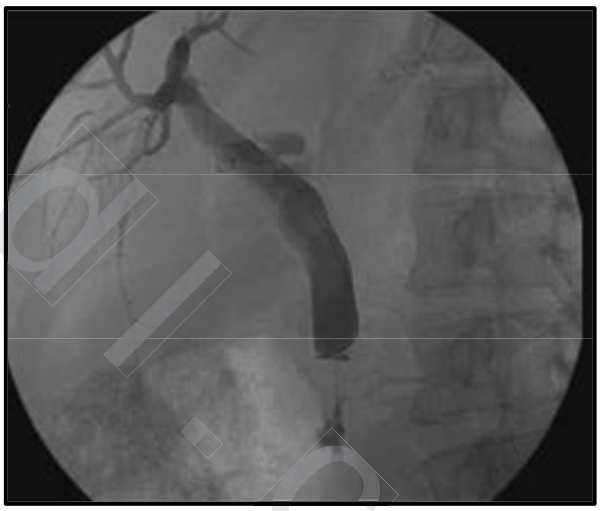

Figure (6): A post-operative distal stricture with shouldering (arrow) seen on percutaneous trans-hepatic cholangiography. [12]

II.Orthotropic liver transplantation (OLT)

Bile duct strictures (biliary strictures) are the most common adverse events of OLT and can be divided in to

1. Early (<60 days after OLT).
2. Early-late (60 days to 1 year)
3. Late (>1 year).

Early strictures are mainly due to technique during creation of the anastomosis, while early late-and late strictures are often the consequence of vascular insufficiency. Early narrowing in a duct to duct anastomosis is most often due to postoperative edema and inflammation and respond well to modest balloon dilatation by ERCP and short term stent placement (3 months) with a low rate of recurrence.[13]

Anastomotic strictures occurring in the early –late period also responds well to short term stent placement(3 to 6 months) but strictures recurrence can occur even years later. Late strictures usually respond well to initial balloon dilation and temporary stent placement (3 months) but the recurrence rate is usually up to 40%.thus repetitive balloon dilatation and longer duration of stent therapy (12 to 24 months)with maximal stents are needed .Non anastomotic strictures are usually multiple and are ischemic in nature with a poor prognosis .in fact ,up to 50 % of patients require retransplantation or they may need multiple endoscopic procedures using balloon dilation, removal of casts and repetitive stent placement are often necessary .Ischemic injuries that involve a large portion of the intrahepatic bile ducts are associated with poor graft survival and often require retransplantation.[14-15]

Table II: Biliary adverse events after liver transplantation.[16]

• Bile leaks	• Anastomotic site • Cystic duct • Cut surface of the liver • Accessory bile ducts • T –tube tract • Incidental intrahepatic injury • Migrated T tube
• Early strictures:	• Mismatched bile duct diameters • Technical errors
• Late strictures	• Anastomotic • Non anastomotic
• Filling defects	• Choleducolithiasis • Sludge • Biliary cast syndrome
• Ampullary obstruction	• Sphincter of oddi dysfunction • Stenosis
• Recurrent biliary disease	• Recurrent malignant neoplasms • Recurrent sclerosing cholangitis

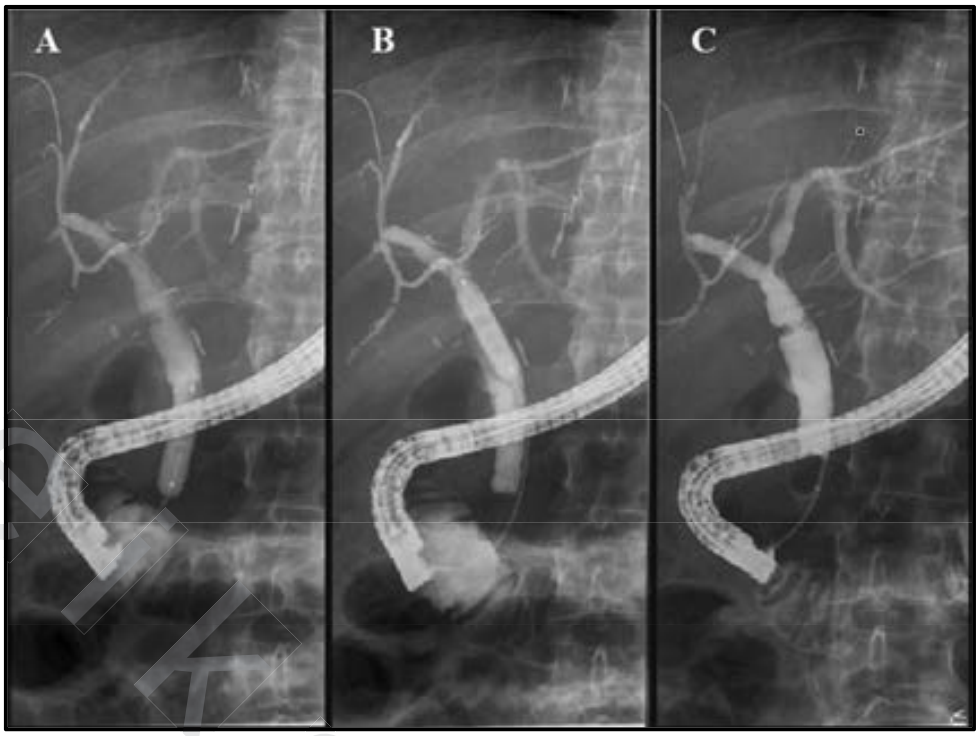

Figure (7): Patient with anastomotic stricture after liver tranplanation.[13]

Classification of post-operative bile duct injuries:

1. Bergman described four types of post-operative bile duct injuries[17]

Table III: Bergman classification of post-operative bile duct injury.

Type	Description
Type A	Cystic duct leaks or leakage from aberrant or peripheral hepatic radicles
Type B	Major bile duct leaks with or without concomitant biliary strictures
Type C	Bile duct strictures without bile leakage
Type D	Complete transection of duct with or without excision of some portion of biliary tree

2. Bismuth classification:[18]

The first classification of bile duct injury is authored by H. Bismuth in 1982. Up to now, a number of classifications have been proposed by different authors. The Bismuth classification is a simple classification based on the location of the injury in the biliary tract. This classification is very helpful in prognosis after repair. This classification included five types of bile duct injuries according to the distance from the hilar structure especially bile duct bifurcation, the level of injury, the involvement of bile duct bifurcation, and individual right sectorial duct.

1. Type I involves the common bile duct and low common hepatic duct (CHD) ＞2 cm from the hepatic duct confluence.
2. Type II involves the proximal CHD ＜2 cm from the confluence.
3. Type III is hilar injury with no residual CHD confluence intact.

4. Type IV is destruction of the confluence when the right and left hepatic ducts become separate.
5. Type V involves the aberrant right sectorial hepatic duct alone or with concomitant injury of CHD.

However, the Bismuth classification does not include the wide spectrum of possible biliary injury.

3. Strasberg classification:[19]

The Strasberg classification is a modification of the Bismuth classifications as shown in table 4, but allows differentiation between small (bile leakage from the cystic duct or aberrant right sectorial branch) and serious injuries performed during laparoscopic cholecystectomy as type A to D. Type E of the Strasberg classification is an analogue of the Bismuth classification.

The major disadvantage of the Strasberg classification is that it does not describe additional vascular involvement at all. For this reason, the Strasberg classification could not demonstrate a significant association between the discrimination of specific injury patterns and liver surgery.

Table IV: Strasberg classification of bile duct injuries.

Type	Description
A	Leak from cystic duct or bile duct of lushka
B	Occlusion of aberrant right hepatic duct
C	Transection without ligation of aberrant right hepatic duct
D	Lateral injury to major bile duct

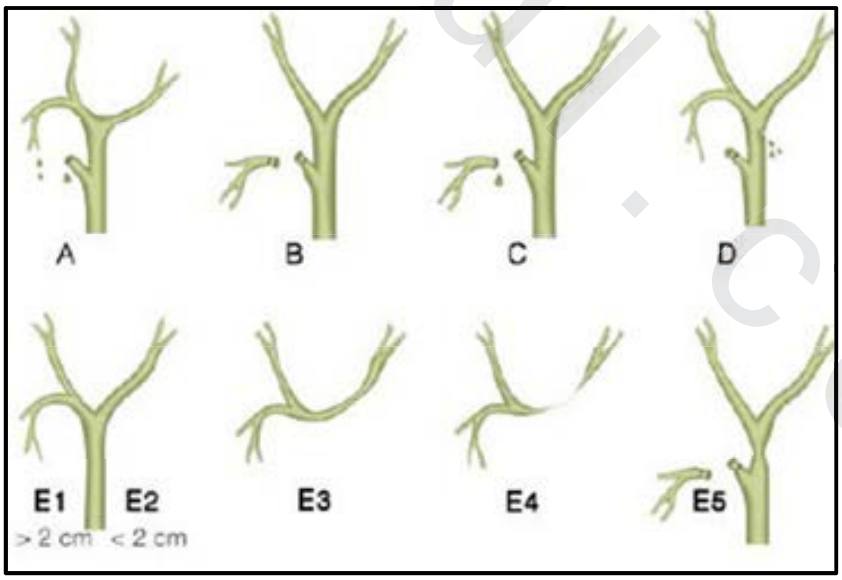

Figure (8): Showing Strasberg classification.[19]

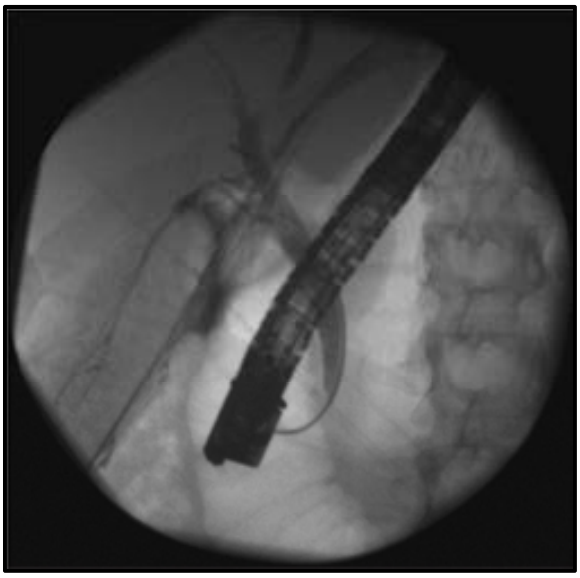

Figure (9): Strasberg type C bile duct injury indicating a leak from the right posterior branch.[19]

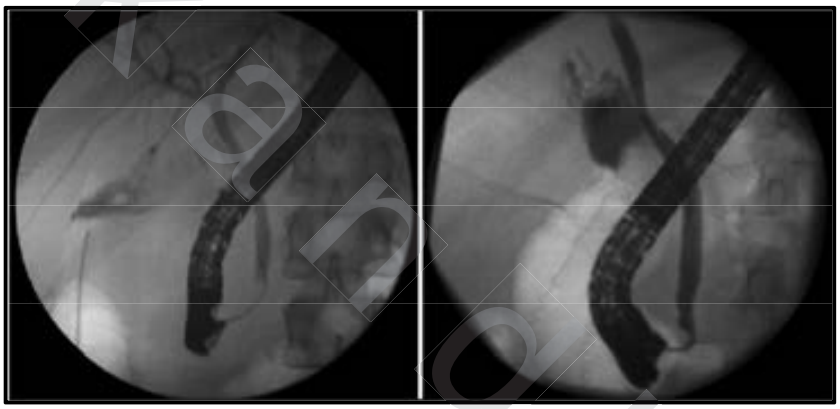

Figure (10): Strasberg type A bile duct injuries indicating a leak from (a) the cystic duct; (b) from the gallbladder bed; this patient ultimately required surgery.[19]

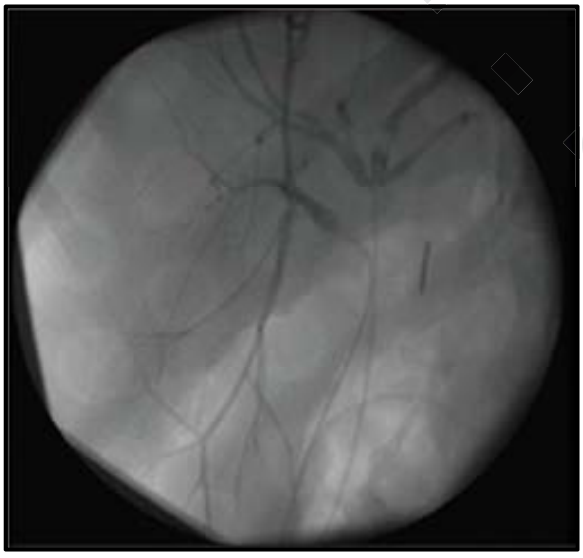

Figure (11): Strasberg type E4 bile duct injury.

4. Hannover classification:[20]

This was published in 2007 but is poorly known in the world literature. It classifies injuries in relationship to the confluence and also includes vascular injuries. It has five subtypes. Type A refers to cystic and/or gallbladder bed leaks. Type B is a complete or incomplete stenosis caused by a surgical staple. Type C represents lateral tangential injuries. Type D refers to complete section of the common bile duct emphasizing their distance to the confluence as well as the hepatic artery and portal vein concomitant injuries. Type E is late bile duct stenosis at different lengths to the confluence.[20]

5. Stewart-Way classification:[21]

This classification involves four types based on the mechanism and anatomy of injury.

Class I: refers to the incomplete section of bile duct with no loss of tissue. It has a prevalence rate of 7%. The first mechanism of injury is a misleading recognition of the common hepatic duct with the cystic duct but is rectified and results in only a small loss of tissue with no complete section of the bile duct. The second mechanism refers to the lateral injury of the common hepatic duct which results from the cystic duct opening extension during cholangiography. The former represents 72% and the latter 28% of class I cases

Class II: is a lateral injury of the common hepatic duct that leads to stenosis or bile leak. It is the consequence of thermal damage and clamping the duct with surgical staples. It has a prevalence of 2% with a concomitant hepatic artery injury in 18% of cases. T-tube related injuries are included within this class.

Class III: is the most common (61% of cases) and represents the complete section of the common hepatic duct. It is subdivided in to type IIIa, remnant common hepatic duct; type IIIb, section at the confluence; type IIIc, loss of confluence; and type IIId, injuries higher than confluence with section of secondary bile ducts.

It occurs when the common hepatic duct is confounded with the cystic duct, leading to a complete section of the common hepatic duct when resecting the gallbladder. A concomitant injury of right hepatic artery occurs in 27% of cases.

Class IV: describes the right (68%) and accessory right (28%) hepatic duct injuries with concomitant injury of the right hepatic artery (60%). Occasionally it includes the common hepatic duct injury at the confluence (4%) besides the accessory right hepatic duct lesion. Class IV has a prevalence of 10%.[21]

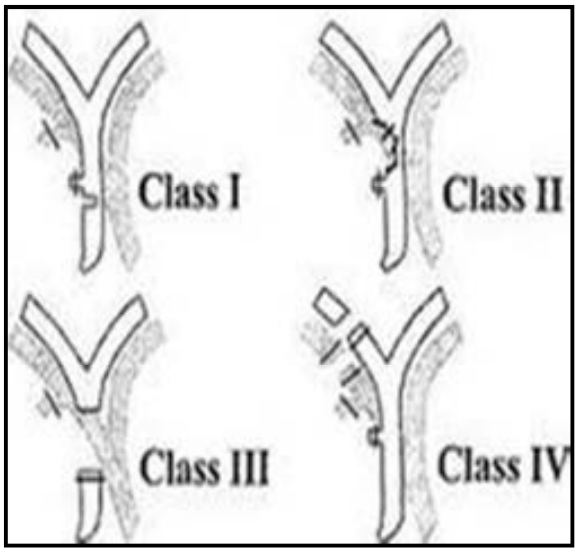

Figure (12): Stewart –Way classification of laparoscopic bile duct injuries.[21]

Diagnosis

The clinical diagnosis of postoperative biliary stricture is usually suspected by the onset of either symptomatic or biochemical cholestasis in the early or the late postoperative period, approximately 10% of postoperative bile duct strictures present within 1 week of surgery and 70 % to 80 % present within 6 to 12 months of surgery, in the first instance, ultrasound examination is performed to confirm biliary dilatation and may suggest the level of biliary obstruction, MRCP is a useful non-invasive diagnostic modality for accurately delineating the biliary anatomy and the site of stenosis and for planning definitive therapy strictures can also be found during ERCP performed mostly for removal of CBD stones.

Management

Traditionally post-operative bile duct strictures were managed surgically and the role of ERCP was limited to the diagnosis and definition of the level and the extent of the stricture. With the increasing use of ERCP for the treatment of the acute adverse events of cholecystectomy, therapeutic ERCP has been extensively adopted to manage postoperative strictures and other benign biliary strictures, percutaneous trans-hepatic therapy with balloon dilatation of the stricture is limited by low success rate, high stricture recurrence rate and high adverse events.

The high recurrence rate following percutaneous trans-hepatic pneumatic dilation is most likely due to forceful disruption of the scar which can add further traumatic damage to the tissue and consequent development of a new fibrotic reaction so these technique are now usually preserved for failed endoscopic procedures or for rendez vous during endoscopy.[22]

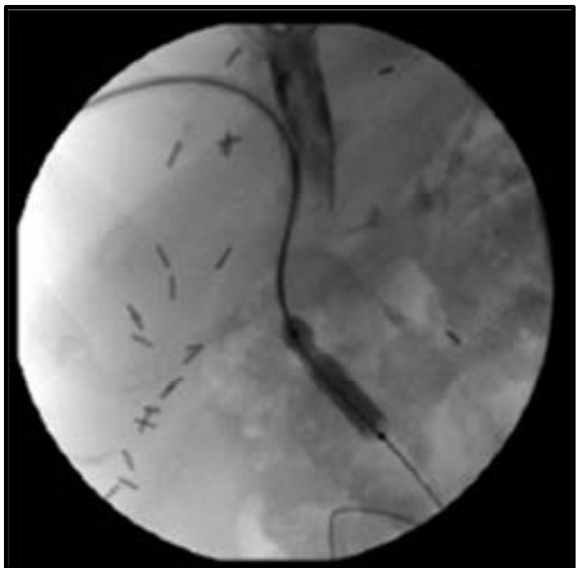

Figure (13): Percutaneous trans-hepatic cholangiogram with balloon dilation of a postoperative bile duct stricture.[22]

Techniques of ERCP in management of post-operative bile duct injury:[23-26]

1. Decreasing intrabiliary pressure

The first aim is to decrease the tone of sphincter of oddi, which diverts bile flow away from the leak site. This can be achieved with biliary endoscopic sphincterotmoy (ES), stent placement alone is preferred in patients at high risk for post ES bleeding.[23]

2. By passing bile flow

In addition to reducing the pressure, the stent diverts bile toward the papilla and reduces flow through the leak site. This contributes indirectly to the closure of the leak. Considering the low morbidity of plastic stents, it is recommended the combined use of ES and stent placement to maximally reduce intrabillary pressure. Traditionally, plastic stents have been used but covered self-expandable metal stents (SEMS) have recently been used. Bio-absorbable self-expandable stents may be an option in the future and would eliminate the need for removal.[24]

Nasobiliary tubes can also be used as an alternative to stent placements in the treatment of biliary leaks after surgery, advantages include avoidance of sphincterotomy, easy removability, and ability to obtain interval tube cholangiogram to asses leak closure, however, because of patient discomfort and potential for dislodgement, nasobiliary tubes are not routinely used.[24]

3. Sealing the leak

In patients with biliopleural fistulae, negative pressure pulls bile into thoracic cavity, application of sealants may be necessary to obtain prompt control of the leak. ERCP can allow application of sealants to close the leak, however, because of the theoretical risk of glue pulmonary embolism, it is reserved for highly selected cases of biliopleural fistulae and bilioperitoneal fistulae refractory to combined treatment with ES and plastic stent placement.[25]

4. Stricture dilatation

Benign biliary strictures require dilation followed by multiple stent placements and exchanges.[26]

III. Chronic pancreatitis

Is a common inflammatory disease characterized by anatomical and functional alterations in pancreas and surrounding tissues, including biliary tract.[27] Its incidence is around 6-8/100,000 and is slightly rising in western countries.[28] Alcohol consumption is the cause in about 70-80% of CP, 20% of the cases are idiopathic, and 5-10% are of an autoimmune or hereditary form.[29] CP induced biliary strictures are seen in 6-23% of patients and account for approximately 10% of all benign biliary strictures.[30] CP is associated with an increased risk of developing pancreatic cancer. In the majority of cases pain is the major clinical symptom and is present early in the course of the disease.[31] Patients with CP have also shorter life expectancy than the normal population, mainly due to non-pancreatic effects of Alcohol and smoking.[32]

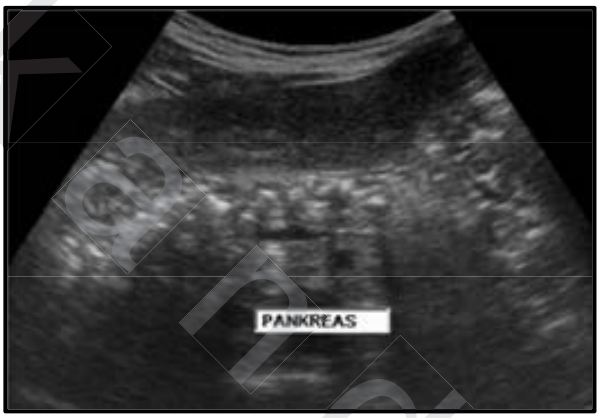

Figure (14): Ultrasound image of patient with chronic pancreatitis.[32]

IV. Primary sclerosing cholangitis

Is a chronic inflammatory disease of the biliary tree .it is characterized by stricturing and dilatation of the intrahepatic and /or extra hepatic bile ducts, with concentric obliterative fibrosis of intrahepatic biliary radicles ,PSC is closely associated with inflammatory bowel disease ,particularly ulcerative colitis which is approximately found in two thirds of northern European PSC patients.[33].

The disease leads to chronic cholestasis but patients may remain asymptomatic at presentation ,diagnosed by abnormal liver functions tests, particularly elevation of the alkaline phosphatase ,or they can present with pruritis, fatigue, right upper quadrant pain and jaundice ,as the disease progress, symptoms of cirrhosis can be manifested .PSC is associated with an un predictable risk of developing cholangiocarcinoma in up to 30% of patients .The etiology and the pathogenesis are unclear but it is likely an immune mediated disease involving an exaggerated cell mediated immune response leading to chronic inflammation of the biliary epithelium.[34]

PSC is diagnosed by radiographic imaging of the biliary tree. this has traditionally been performed using ERCP but more recently MRCP is thought to be as sensitive as ERCP in the diagnosis of PSC if the best equipment and operator are available

Liver biopsy has a limited role in diagnosis but is a useful adjunct to determine the stage of the disease. Histology can range from normal to frank biliary cirrhosis with the typical appearances being portal inflammation, concentric onion skin, periductal fibrosis and periportal fibrosis developing in to septal and bridging necrosis.[35]

The endoscopists role in PSC involves diagnosis of cholangiocarcinoma, therapeutic intervention of strictures in the bile duct including dilatation and stenting, managing bile duct stones that can complicate PSC and differentiating between benign and malignant strictures.[36]

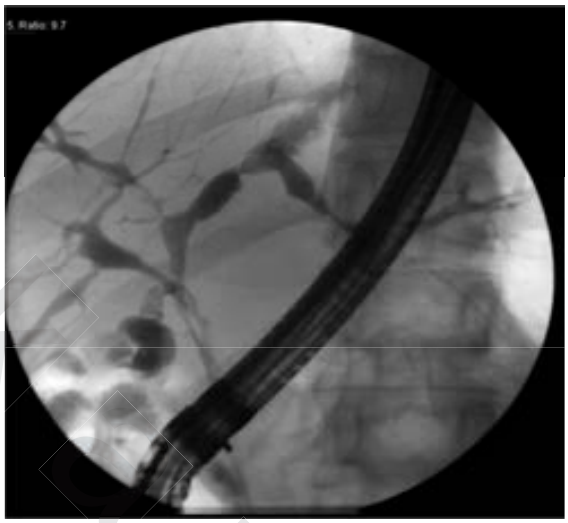

Figure (15): ERCP image of primary sclerosing cholangitis.[35]

V. HIV cholangiopathy

Patients with HIV cholangiopathy usually have advanced acquired immunodeficiency syndrome (AIDS) with CD4 lymphocyte counts less than 100/mm^3 and poor long-term survival prognoses. Cryptosporidium and cytomegalovirus may be responsible for more than 90% of cases. Other causes of HIV cholangiopathy, occurring in fewer than 10% of patients, include microsporidia. Mycobacterium avium-intracellulare (MAI), Cyclospora, Isospora and Cryptococcus. Most patients present with severe right upper quadrant pain, nausea, vomiting, and fever.Using ERCP, 4 distinct patterns of HIV cholangiopathy have been described, as follows:[37]

1. **Papillary stenosis**: This occurs in approximately 15-25% of patients. A smooth distal tapering of the CBD associated with proximal dilatation to wider than 8 mm is present. Contrast is retained beyond 30 minutes.
2. **Sclerosing cholangitis**: This pattern is observed in 20% of patients and is characterized by focal strictures and dilatations involving intrahepatic and extra-hepatic bile ducts. The caliber of extra-hepatic ducts is normal.
3. **Combined papillary stenosis and sclerosing cholangitis:** This is the most common pattern of HIV cholangiopathy and is observed in more than 50% of cases.
4. **Long strictures of extrahepatic bile ducts**: This pattern is observed in approximately 15% of patients. The strictures are 1-2 cm long and do not have features suggesting another cause, such as previous biliary surgery or pancreatitis.

VI. Mirizzi syndrome

This condition is observed in 1% of patients with long standing gall bladder diseases. Extrinsic compression of the common hepatic duct due to a gallstone impacted in the Hartmann pouch or cystic duct results in jaundice and cholangitis. Repeated episodes of inflammation can lead to formation of a stricture (type I) or pressure necrosis leading to the formation of a cholecystocholedochal fistula (type II).

The condition was classified by McSherry and colleagues in1982 and the modification of the same by Csendes and colleagues in 1989 into classes 1–4 is the currently accepted classification. The Csendes classification of MS is as follows:

Type 1: External compression of the common bile duct – 11%.

Type 2: Cholecystobiliary fistula is present involving less than one-third the circumference of the bile duct – 41%.

Type 3: A fistula is present involving upto two-third the circumference of the bile duct – 44%.

Type 4: A fistula is present with complete destruction of the wall of the bile duct 4%

Type 5: Cholcystoenteric fistula.[38]

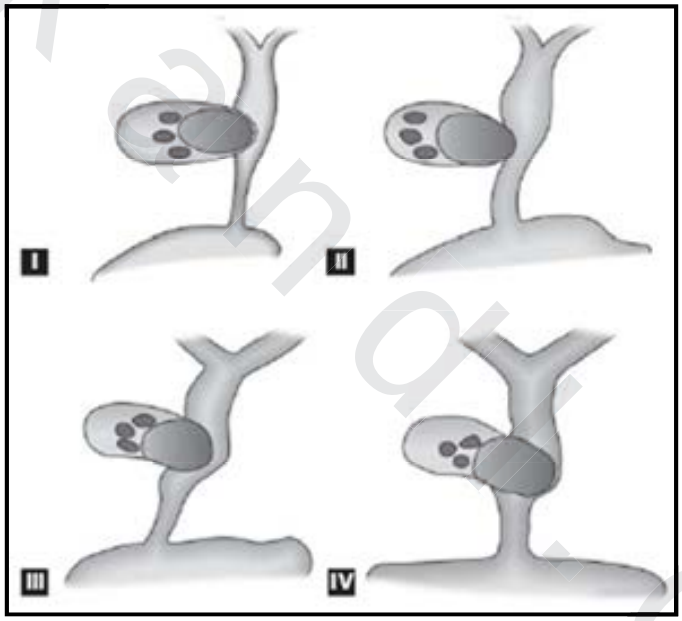

Figure (16): Csendes classification of MS.[38]

Diagnosis

The initial diagnosis of Mirizzi's syndrome should be suggested by the combination of jaundice (+/- cholangitis) and ultrasonographic evidence of proximal duct dilatation, especially when it occurs in an elderly patient. Endoscopic cholangiopancreatography (ERCP) remains the gold standard for the confirmation of the diagnosis; however, magnetic resonance cholangiography has been proposed as a less invasive, equally effective method of preoperative study. Computed tomographic scans provide little additional information except to exclude an associated tumor.[39]

Management

Because of the variability of the underlying disease in Mirizzi's syndrome, treatment must be individualized. In most patients; an open operation is preferred over a laparoscopic procedure because of the extreme anatomic distortion that is present in the triangle of Calot as a result of the intense inflammation.[40]

In patients with type I disease, a top-down, subtotal cholecystectomy should be performed, taking care to avoid damage to the common hepatic bile duct. Any stone(s) should be removed and the distal gallbladder cuff or enlarged cystic duct should be primarily closed with a purse-string suture or stapler. This same approach can also be used for Mirizzi's type II disease; however, control of the associated fistula should be tailored to the individual situation.[41]

Small and intermediate fistulas can be managed with placement of a T-tube through the fistula. Inflammation and stenosis will usually gradually resolve. Large fistulas and/or circumferential destruction of the hepatic duct will usually mandate the use of biliary diversion with a choledochoduodenostomy or a Roux-en-Y choledochojejunostomy. Alternatively, some large defects can be patched with flaps formed from the residual gallbladder wall, but this approach has a higher leak rate and provides less satisfactory long-term results.[42]

Of importance, frozen section analysis of the specimen should be considered in all patients because of a significant association of Mirizzi's syndrome with gallbladder cancer.[43]

Role of ERCP

Finally, non-operative methods should be considered in those patients in whom the operative risk is prohibitive. In this regard, the endoscopic placement of biliary stents can provide long-term decompression of the obstructed duct in the majority of patients. Moreover, in selected instances, stones can be disimpacted using baskets, mechanical lithotripsy, or extracorporeal shockwave lithotripsy. Nonetheless, it is important to remember that not all patients improve with stenting, and long-term complications such as sepsis and secondary biliary cirrhosis can develop.[44]

VII. Choledochal cysts

Choledochal cysts are uncommon anomalies of the biliary system manifested by cystic dilatation of the extra-hepatic biliary tree, intrahepatic biliary tree, or both. This condition is found most frequently in Asian persons and in females. Associated hepatobiliary complications include recurrent cholangitis, bile duct stricture, cholelithiasis, choledocholithiasis, and recurrent acute pancreatitis.[45]

These anomalies are classified according to the system published by Todani and coworkers. Five major classes of choledochal cysts exist (ie, types I-V), with sub-classifications for types I and IV (ie, types IA, IB, IC; types IVA, IVB).[46]

Type I cysts (see image below) are the most common and represent 80-90% of choledochal cysts. They consist of saccular or fusiform dilatations of the common bile duct, which involve either a segment of the duct or the entire duct.

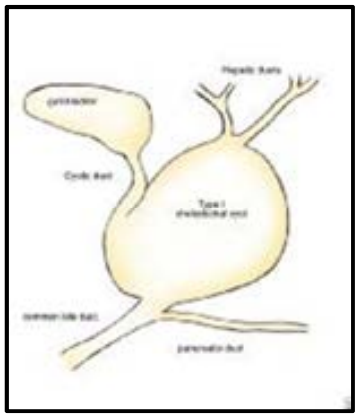

Figure (17): Type I choledochal cyst. [46]

Type IA is saccular in configuration and involves either the entire extra-hepatic bile duct or the majority of it.

Type IB is saccular and involves a limited segment of the bile duct.

Type IC is more fusiform in configuration and involves most or all of the extra-hepatic bile duct.

Type II choledochal cysts (see image below) appear as an isolated diverticulum protruding from the wall of the common bile duct. The cyst may be joined to the common bile duct by a narrow stalk.

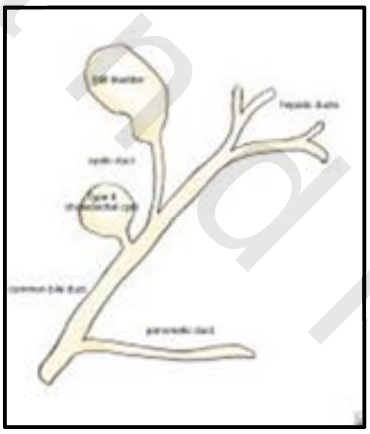

Figure (18): Type II choledochal cyst.[46]

Type III choledochal cysts (see image below) arise from the intraduodenal portion of the common bile duct and are described alternately by the term choledochocele.

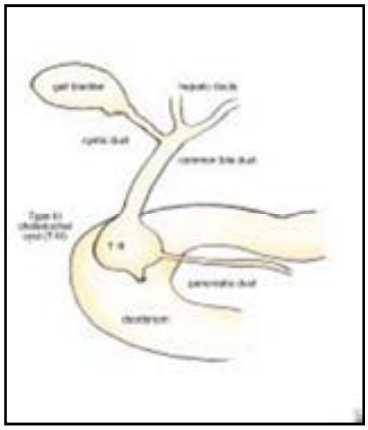

Figure (19): Type III choledochal cyst (choledochocele).[46]

Type IVA cysts (see image below) consist of multiple dilatations of the intrahepatic and extra-hepatic bile ducts. Type IVB choledochal cysts are multiple dilatations involving only the extra-hepatic bile ducts.

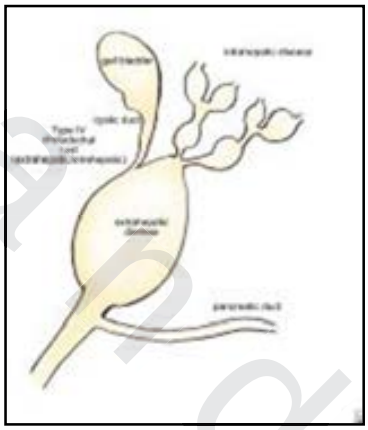

Figure (20): Type IV choledochal cyst (extra-hepatic and intrahepatic disease). [46]

Type V (Caroli disease) cysts (see image below) consist of multiple dilatations limited to the intrahepatic bile ducts.

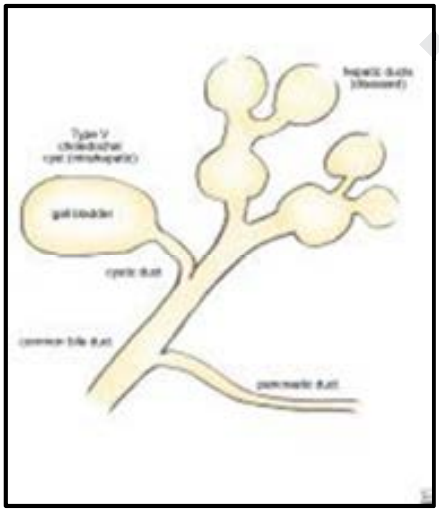

Figure (21): Type V choledochal cyst (intrahepatic, Caroli disease).[46]

Although pancreatitis has been reported to occur in association with all types of extra-hepatic choledochal cysts it occurs most commonly with type III choledocholcele, moreover choledochceles are rarely identified by standard radiologic imaging while other extra-hepatic choledochocele are typically suspected or recognized by abdominal ultrasound or CT scan, idiopathic acute pancreatitis has been reported in 30% to 70% of patients found to have choledochocele.(47)

Diagnosis

Choledochocele are usually diagnosed endoscopically ,the papilla has a bulging appearance but is soft pillow sign when probed with a catheter tip .a rounded cystic structure can be demonstrated at the terminal end of the common bile duct following contrast injection in to the biliary tree with associated progressive enlargement or ballooning of the papilla.

Non-invasive and less invasive tests using EUS and MRCP have been reported, it was suggested that MRCP may supersede the diagnostic role of ERCP for the patients with choledochal cysts however MRCP showed limited capacity to detect minor ductal anomalies or small choledochocele.(48)

Treatment

Surgical therapy either by excision or sphincteroplasty has been the traditional approach to choledochoceles, however endoscopic therapy appears to be an effective treatment on the majority of patients with choledochoceles, the endoscopic approach is to unroof the cyst and perform biliary sphincterotomy.(49)

VIII. Recurrent pyogenic cholangitis

This condition (previously known as Oriental cholangiohepatitis) and hepatolithiasis are prevalent in Southeast Asia and present a difficult management problem. Recurrent pyogenic cholangitis is a condition characterized by repeated attacks of bacterial infections of the biliary tract.(50)

It is believed that the inciting event is entry of bacterial flora in to the biliary tree causing infection and inflammation and through bacterial deconjugation of bilirubin diglucournide formation of biliary stones occur, persistent inflammation results in biliary stricture and stasis of the bile in the biliary tree which encourages further formation of stones leading to vicious cycle of repeated or persistent inflammation and infection.

There have been reports linking helminthiasis to RPC, ascaries lumbricoides and clonorchis sinensis worms have been identified in the biliary tract of patients with RPC.(51)

Diagnosis and management

The hallmark of RPC is the presence of both stones and strictures which can be located in both extra-hepatic and intrahepatic ducts.

Patients with RPC often present with acute cholangitis which may be the first attack or recurrent episodes.(52)

These patients may develop septic shock rapidly. Initial management includes intravenous fluid replacement and the institution of intravenous, potent broad spectrum antibiotics. Emergency surgical decompression may be necessary in some patients but carries with it a high postoperative morbidity and mortality rate.(53)

IX. Radiation

Bile duct strictures (biliary strictures) can occur as a late complication of radiation therapy in the upper abdomen for cancer or lymphoma, sometimes presenting many years after treatment.[54]

X. Blunt abdominal trauma

This can lead to bile duct strictures, which usually have a delayed presentation.

XI. Polyarteritis nodosa and systemic lupus erythematosus (SLE)

These are autoimmune diseases involving small- to medium-sized arteries. They can present (rarely) as extrahepatic biliary obstruction secondary to biliary strictures.

XII. Tuberculosis and Histoplasmosis

These conditions have rarely been reported to cause bile duct strictures (biliary strictures) in individuals who are immunocompetent.[55]

XIII. Chemotherapeutic drugs

Hepatic artery infusion of 5-fluorodeoxyuridine (FdUrd, FUDR) or other chemotherapeutic drugs may cause bile duct strictures (biliary stricture)

XIV. Endoscope-related strictures

Post-endoscopic sphincterotomy stricture is possible.

XV. Miscellaneous

Strictures have been described in association with duodenal diverticulum, Crohn disease, and hepatic artery aneurysm, cystic fibrosis with liver involvement, eosinophilic cholecystitis, and cholangitis.

Malignant causes of bile duct strictures (biliary strictures)

Malignant strictures of the pancreaticobiliary tree are often difficult to diagnose and hence these factors contribute to the poor prognosis of these tumors. Jaundice is the most common presenting sign and symptom of malignant biliary obstruction .The causes of malignant biliary obstruction include pancreatic cancer, carcinoma of the ampulla of Vater, gallbladder cancer, Distal cholangiocarcinoma and metastatic diseases that involves the head of the pancreas or the common bile duct (CBD) (table V)[56]

Causes of malignant biliary strictures:

1. Pancreatic carcinoma.
2. Ampullary carcinoma.
3. Cholangiocarcinoma.
4. Gall bladder carcinoma.
5. Hepatocellular carcinoma.
6. Metastatic diseases.

1. Pancreatic cancer

The most common cause of malignant distal biliary obstruction is pancreatic cancer. In the united states an estimated 43,920 new pancreatic cancer will occur in 2012 with an estimated 37,390 deaths expected to occur from this condition. The incidence rate of pancreatic cancer has been increasing by 1.5% per year since 2004, with an increase in mortality rates of 0.4% per year during this period. By 2012 estimates, pancreatic cancer ranks among the top 10 newly diagnosed cancer in the united states in both sexes, and it ranks fourth in cancer-related deaths in both sexes. Although globally pancreatic cancer ranks among the top 10 cancer-related deaths, mainly because of its exceptionally high mortality.[57]

Risk factors

Advancing age is a recognized risk factor for pancreatic cancer. The median age at diagnosis of pancreatic cancer in the united states is 72 years. About 5%to 10% of patients develop pancreatic cancer before they are age 50 years, but this group is more likely to include those with predisposing genetic disorders or those who have undergone treatments for cancer such as previous radiation.[58]

Heavy consumption of alcohol (three or more srinks per day or greater than or equal to (30 to 40g of alcohol per day) is associated with a 22% increase in the risk of pancreatic cancer. Cigarette smoking has been strongly associated with pancreatic cancer and the risk increases by 70% to 100% over nonsmokers.[59]

Table V: Causes of malignant biliary obstruction.

Primary Cancer	Metastatic Cancer
Pancreatic cancer	Gastric cancer
Caricnoma of ampulla of vater	Colon cancer
Cholangiocarcionoma	Breast cancer
Gallbladder carcinoma	Lung cancer
	Renal cell carcinoma
	Melanoma
	Hepatocellualr cancer
	Malignant lymphadenopathy

Chronic pancreatitis, although rare, increases the risk for developing pancreatic cancer other implicated risk factors for pancreatic cancer include vitamin D and ultraviolet B (UVB) radiation, occupational exposure, and obesity.

Genetic factors that increase the risk of pancreatic cancer include familial atypical multiple mole melanoma (FAMMM) syndrome, hereditary pancreatitis, peutz-jeghers syndrome, familial pancreatic cancer, cystic fibrosis, familial a adenomatous polyposis, and hereditary non-polyposis colorectal cancer (HNPCC) syndrome. A family history of pancreatic cancer is associated with a two fold increase in the pancreatic cancer risk.[60]

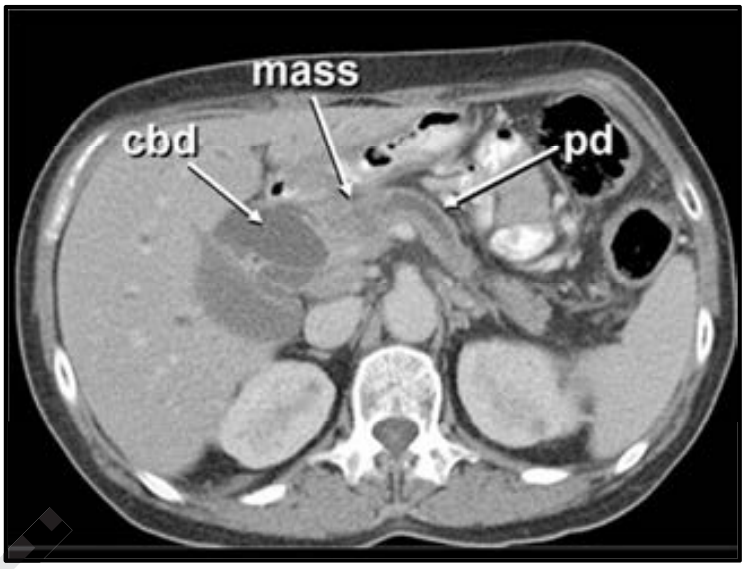

Figure (22): CT image of cancer head of pancrease.[58]

2. Ampullary carcinoma

Ampullary Caricnoma often presents with obstructive jaundice and it is suspected if imaging studies detect dilation of the pancreaticobiliary ducts. Ultrasound is not very sensitive to detect ampullary carcinoma due to the small size of the tumor. In addition, overlying bowel gas limits the views of the retroperitoneal structures. Thus ultrasound relies more on indirect evidence such as dilated bile ducts. Computed tomography (CT) scan provides more accuracy than ultrasound in this regard but still a substantial number of lesions could be missed.[61]

Magnetic resonance cholangiopancreatography (MRCP) is another noninvasive technique and is superior to CT scan in detecting biliary obstruction. However, MRCP cannot differentiate between tumors and another benign causes of ampullary obstruction such as stones or benign strictures. ERCP can be both diagnostic by detecting an ampullary mass and providing tissue samples and therapeutic for relieving obstructive jaundice. EUS and ERCP are comparable in terms of detecting ampullary cancers.[62]

EUS is the most accurate imaging modality to provide information about the local tumor staging of ampullary neoplasms when cure appears feasible through surgery, the choice of surgery such as local resection versus a more radical surgery such as pancereaticoduodenectomy is determined by the staging information obtained from the noninvasive techniques discussed above.[63]

Clinical picture of cancer pancreas is summarized in table

Table VI: Common symptoms associated with pancreaticobiliary malignancies.

Symptoms	signs
Symptoms of biliary obstruction Jaundice Pale stools Steatorrhea Dark urine Generalized pruritus Nausea	Sclera icterus Signs of nutritional deficiency
Constitutional symptoms Weight loss Anorexia	Organomegaly Liver Gallbladder Lymph nodes
Pain Epigastric or right upper quadrant abdominal pain Back pain (mostly advanced disease)	Trousseau sign: swollen blood vessels
Dyspepsia From gastric outlet or duodenal obstruction	

3. Cholangiocarcinoma

This cancer arises from the biliary epithelium and is usually seen in association with choledochal cysts, PSC, chronic ulcerative colitis, and infestation by liver flukes. For unclear reasons, the incidence of intrahepatic cholangiocarcinoma has been rising over the past 2 decades in Europe, North America, Asia, Japan, and Australia, whereas rates of extra-hepatic cholangiocarcinoma are declining internationally.(64)

Cholangiocarcinoma is more common in the upper portions of the biliary tree (hilar or Klatskin tumor) than in the lower portions of the biliary tree (distal bile duct cancer), but it can also be diffuse in 10% of cases. Cholangiocarcinoma is traditionally classified anatomically as intrahepatic or extra-hepatic, with extra-hepatic disease further classified as proximal (hilar) or distal.(65)

Some of the early studies made a distinction between lesions in the middle third (below the cystic duct but not intrapancreatic) and lower third (the intrapancreatic portion) of the bile duct. Because malignancies in the middle third of the extrahepatic bile duct are distinctly rare, more recent reports favor the classification of middle third lesions as distal disease.(65)

The original report by Klatskin in 1965 described cancer of the perihilar region, which currently accounts for about 60% to 80% of all cholangiocarcinomas. Subsequently, hilar malignancies have been further classified based on the Bismuth-Corlette system, which includes all extra-hepatic disease down to the confluence of the cystic and common hepatic ducts. Based on location, into the following 5 types.(66)

Type 1: This is a low common hepatic duct stricture. At least 2 cm of the hepatic duct is intact.

Type 2: This is a mid-common hepatic duct stricture. The hepatic duct stump is smaller than 2 cm.

Type 3: This is a hilar stricture. The common hepatic duct is not involved, but the confluence of right and left hepatic ducts is intact.

Type 4: In this type of bile duct stricture, the hilar confluence is destroyed. The right and left hepatic ducts are separated.

Type 5: The aberrant right sectorial duct is involved, alone or with the CBD.

The modified Bismuth and Corlette classification of hilar cholangiocarcinoma is the most widely adopted anatomic classification of this tumor. The following 4 types are recognized:[67]

Type 1: The confluence of the hepatic ducts is not involved, but the tumor is generally within 2 cm of the hilum.

Type 2: The obstruction is limited to the confluence of the right and left hepatic ducts.

Type 3a: The confluence is involved, with extension of the tumor into the right hepatic duct.

Type 3b: The confluence is involved, with extension of the tumor into the left hepatic duct.

Type 4: The tumor is multicentric or extends into the right and left hepatic ducts.

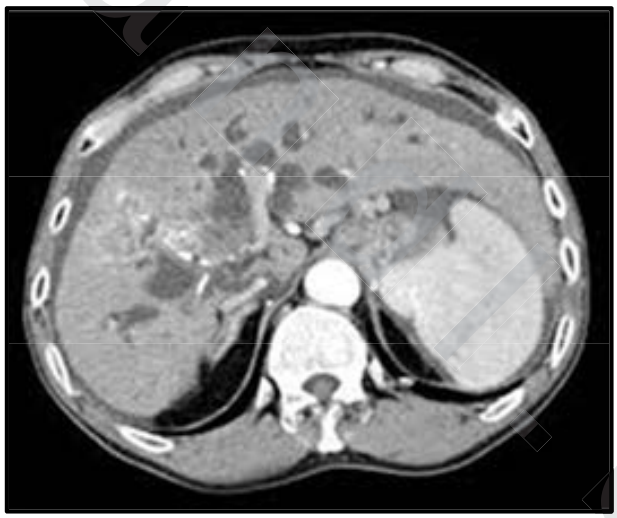

Figure (23): CT image of cholangiocarcinoma.[66]

The majority of cholangiocarcinoma are adenocarcinoma (>90%)squamous cell carcinoma account for most of the remaining cases .adenocarcinoma are divided in to nodular, sclerosing and papillary types, both the nodular and the sclerosing tumors have lower resection cure rates.[68]

Tumors usually do not become symptomatic until they obstruct both the left and the right biliary systems. The degree of symptoms and jaundice directly correlate with the level of the obstruction. Most advanced biliary obstruction often presents as fatigue, anorexia, painless jaundice. Other common symptoms include pruritis(66%),abdominal pain(30to 50%),weight loss (30 to 50%)and fever (10 to 20%).[69]

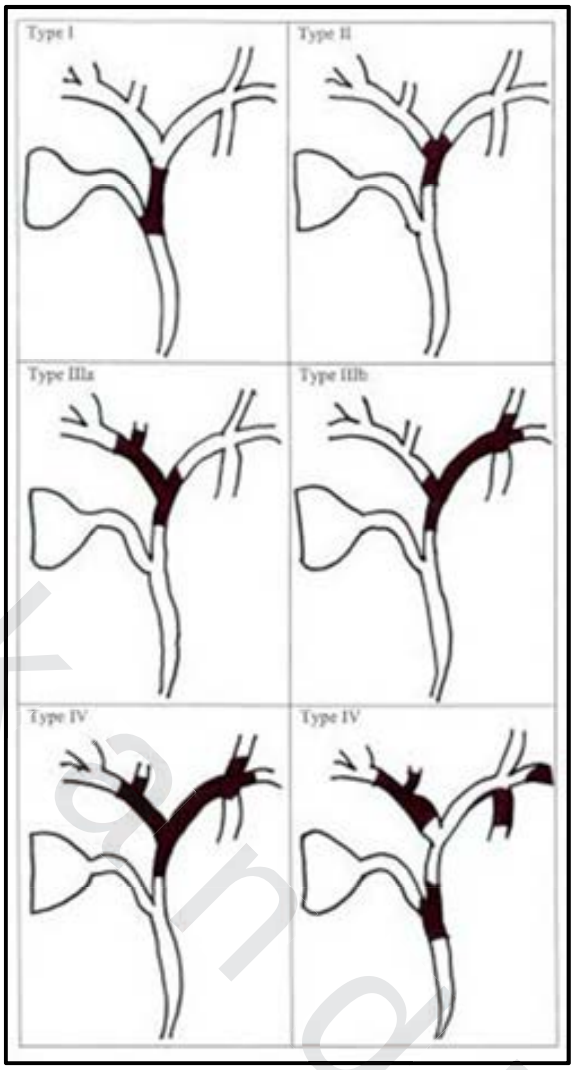

Figure (24): Bismuth classification of cholangiocarcinoma.[66]

4. Gallbladder carcinoma

Extension of the cancer beyond the gallbladder can cause long bile duct strictures (biliary strictures) and obstruction, and it is a poor prognostic sign. In the United States, gallbladder cancer is the fifth most common gastrointestinal malignancy, with 6000 new cases each year. Gallbladder cancer occurs at a higher frequency in Native Americans and in people from Asia, Africa, and Latin America.[70]

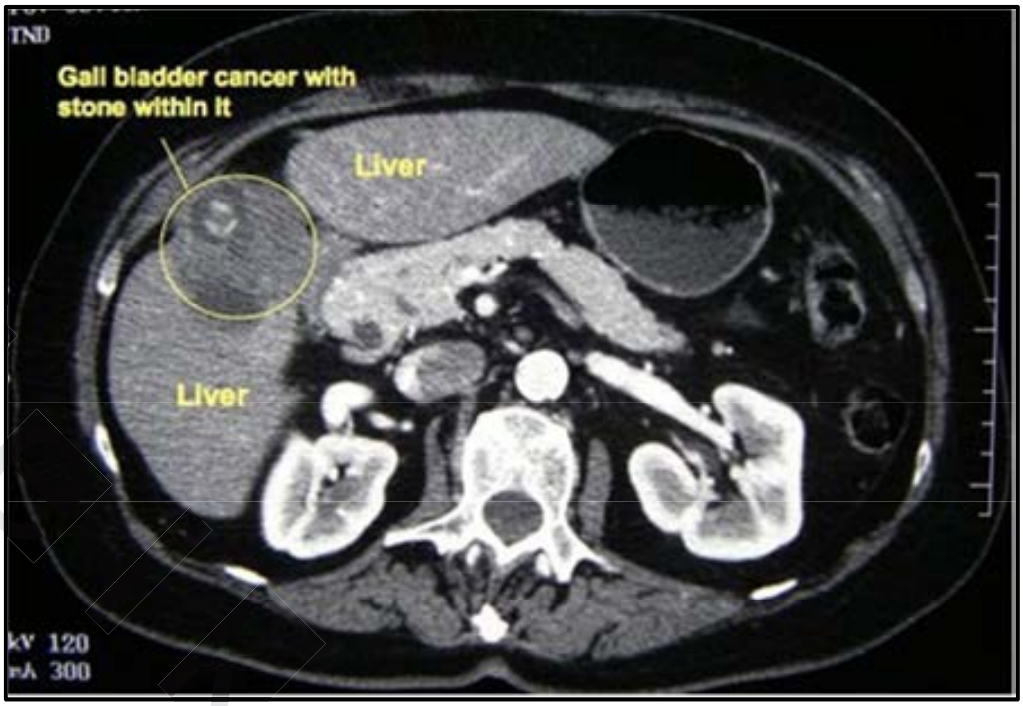

Figure (25): CT image of cancer gall bladder.[70]

5. Hepatocellular cancer

This is the most common primary liver malignancy. Hepatocellular cancer is the fourth leading cause of cancer-related death in the world and the third most common among men. Hepatocellular cancer is more common in the Far East than in the United States and is usually associated with cirrhosis resulting from hepatitis B or hepatitis C. The condition can present (rarely) with features of invasion of the extra-hepatic biliary system as the predominant clinical manifestation.[71]

6. Metastatic disease

The cancers that metastasize and cause malignant biliary tract obstruction in order of frequency are gastric, colon, breast, colon, breast, and lung cancers. Others include renal cell carcinoma, melanoma. Occasionally malignant lymphadenopathy can cause malignant biliary obstruction. These lesions may cause either extrinsic of the bile duct. Often a primary source of cancer is known, making diagnosis easy. In other instances the lesion may be discovered when endoscopic or surgical management of biliary obstruction is attempted. Imaging modalities such as CT scan and MRI may be useful in determining the level of the obstructive jaundice. Due to advanced disease, except in very limited cases, palliation becomes the only option available to these patients.

Clinical picture

A. Manifestations of cholestasis

In the absence of symptoms of the primary disease, most patients with bile duct strictures remain asymptomatic until the lumen of the bile duct is sufficiently narrowed to cause resistance to the flow of bile. Accumulation of bilirubin in the bloodstream and subsequent deposition in the skin causes jaundice (icterus).

Conjunctival icterus is generally a more sensitive sign of hyperbilirubinemia than generalized jaundice. Total serum bilirubin values are normally 0.2-1.2 mg/dL. Jaundice may not be clinically recognizable until levels are at least 3 mg/dL. Urine bilirubin is normally absent. When it is present, only conjugated bilirubin is passed into the urine.

This may be evidenced by dark-colored urine seen in patients with obstructive jaundice or jaundice due to hepatocellular injury. However, reagent strips are very sensitive to bilirubin, detecting as little as 0.05 mg/dL. Thus, urine bilirubin may be found before serum bilirubin reaches levels high enough to cause clinical jaundice.

The lack of bilirubin in the intestinal tract is responsible for the pale stools typically associated with biliary obstruction. The cause of itching (pruritus) associated with biliary obstruction is not clear. Some believe it may be related to the accumulation of bile acids in the skin. Others suggest it may be related to the release of endogenous opioid.[72]

Occasionally, patients may have intermittent episodes of right upper quadrant pain (biliary colic), with or without laboratory features of biliary obstruction. On occasion, a patient may present dramatically with sepsis and hypotension due to ascending cholangitis.

The clinical manifestations of obstructive jaundice may develop rapidly or slowly depending on the underlying cause with chronic cholestasis, xanthomas appear around the eyes, chest, back, and on extensor surfaces. Weight loss and deficiency of calcium and fat-soluble vitamins can occur. Patients also may report anorexia, nausea, vomiting, and cachexia. Insidious weight loss may suggest malignant obstruction.

B. Manifestations of cholangitis:

Cholangitis occurs in the presence of partial or complete obstruction of the common bile duct (CBD), with increased intraluminal pressures, bacterial infection of the bile with multiplication of the organisms within the duct, and seeding of the bloodstream with bacteria or endotoxin. Cholangitis can rapidly become a life-threatening condition.

Clinical presentation varies, with the Charcot triad of fever and chills, jaundice, and right upper quadrant abdominal pain occurring in most patients. A smaller proportion of those with cholangitis may also have altered mental status and hypotension (ie, Reynold pentad).[73]

Physical examination

Asymptomatic patients with bile duct strictures may have unremarkable physical examination findings. Most patients with tight strictures have clinically apparent jaundice. Excoriations of the skin may be seen in patients with pruritus. Patients presenting with cholangitis may also have fever and right upper quadrant tenderness in addition to jaundice (ie, Charcot triad), hypotension, and altered mental status (ie, Reynold pentad).[74]

The presence of palmar erythema, Dupuytren contracture, gynecomastia, spider angiomas, ascites, and splenomegaly may suggest underlying cirrhosis and portal hypertension. A palpable, nontender gallbladder and jaundice are usually observed in patients with malignant obstruction. The presence of these symptoms is called the Courvoisier sign. An enlarged nodular liver may indicate malignancy involving the liver or a large right upper quadrant mass may indicate a malignancy involving the gallbladder. The presence of a friction rub or bruit may also suggest malignancy.[75]

Patients with a major surgical injury to the bile duct and those with recurrent strictures and interventions may have evidence of a bile leak in the form of a biliary fistula, biliary peritonitis, or a biloma. These complications usually become evident early in the postoperative period but sometimes appear weeks to months later. Attention should be given to the nutritional status of the patient. Features of fat-soluble vitamin deficiency may be present and should be sought.(76)

Investigations

I. Laboratory Studies

A. Investigations to asses cholestasis

Integral to the biochemical evaluation of obstruction are the bilirubin and liver associated enzymes .these generally include alkaline phosphatase(AP), alanine aminotransferase and aspartate aminotransferase. The principle markers of cholestasis are **bilirubin** and **AP,** the total bilirubin present in the serum represents a balance between input from production and output from hepatobiliary removal .In obstructive jaundice the serum bilirubin is principally in the conjugated form (water soluble).

Hepatobiliary AP is present on the apical membrane of the hepatocyte and in the luminal bile duct epithelium. Increase in AP results from increase synthesis and release in to the serum.as a result, level may not rise until 1 to 2 days after biliary obstruction occurs. In addition, the enzyme has a half-life of 1 week and may therefore remain elevated for several days even after the resolution of biliary obstruction.(77)

Levels of AP up to 3 times normal are relatively nonspecific and occurs in a variety of liver disease, however higher elevations are more specific for biliary obstruction (intrahepatic or extra-hepatic) and infiltrating liver diseases.as AP can be produced and occur in sources outside the liver , it may be necessary in certain instances to use other biochemical tests such as AP isoenzymes or the gamma-glutamyl transpeptidase or 5 – nucleotidase to confirm the hepatobiliary etiology of an elevated AP.

The serum aminotransferase include AST and ALT. transient elevations within 1 to 2 days with levels in to the thousands may occur in acute CBD obstruction , from trauma, or typically in the instance of choledocholithiasis with subsequent rapidly declining .Aminotransferase levels may also rise from other subacute or chronic obstructions but typically remains below 500 iu/dl.(78)

It is difficult to interpret the predictive models using these markers in evaluating obstruction from stones as the results vary among studies. In general there is an increased like hood for CBD obstruction with abnormalities in bilirubin, AP, and transaminase levels. With these studies in mind there have been reports of patients with normal LFTS despite both dilated ducts and strictures.(79)

In malignant bile duct strictures with complete obstruction, the level of total serum bilirubin is generally much higher than that observed in benign strictures, and a bilirubin level of greater than 20 mg/dL is highly suggestive of malignant obstruction. Again, in malignant strictures causing only partial obstruction (eg, Klatskin tumor), a rise in the alkaline phosphatase level may not be accompanied by a rise in the bilirubin level. Other laboratory abnormalities sometimes observed are anemia, elevated amylase and lipase levels, and an elevated erythrocyte sedimentation rate (ESR) and lactic dehydrogenase (LDH) level.(80)

The prothrombin time (PT) and international normalized ratio (INR) may be prolonged and can usually be normalized with parenteral administration of vitamin K. Total cholesterol and lipoprotein levels may be elevated in patients with chronic cholestatic disorders.[81]

B. Investigations to assess the cause

Several tumor markers may be helpful in the diagnosis of malignant bile duct strictures:

1- A serum carbohydrate antigen 19-9 (CA19-9): Obstructive jaundice is frequently associated with false CA19-9 elevation in benign conditions. n the presence of successfully drained obstructive jaundice, CA19-9 serum levels that remain unchanged or measure more than 90 U/mL are strongly indicative of a malignant cause of obstruction value of greater than 100 U/mL is 55-65% sensitive for cholangiocarcinoma and gallbladder cancer. CA 19-9 should be used in contemporary algorithms for the diagnosis of pancreatic cancer. Elevated values should be repeated after relief of jaundice.[82]

2- Elevated serum carcinoembryonic antigen levels may be present in 50-70% of cases of pancreatic cancer, and alpha-fetoprotein (AFP) levels are elevated in as many as 60% of cases of hepatocellular carcinoma., it was also found that CEA is secreted in high levels from mucinous pancreatic cystic lesions as opposed to serous cystadenoma ,it is thought that higher level of CEA suggest a higher likelihood of mucinous pancreatic neoplasm ,studies have shown that fluid CEA levels >200ng/ml are highly sensitive and specific for mucinous cystic lesionsbut cannot differentiate between benign and malignant lesions.[83]

3- Serum trypsinogen-2 is a useful marker for diagnosing patients with cholangiocarcinoma. It is unclear whether trypsinogen-2 could be a new method to screen PSC or whether tumor marker combinations would be more useful.[84]

II. Radiological investigations

A. Ultrasonography

US generally is considered the imaging modality of choice for the initial screening of biliary disorders. US does not use ionizing radiation to create the image, and it is the least invasive radiologic technique for imaging the biliary tract. The technique is portable, quick, and the technique of choice in pregnant women and in patients with contrast allergies. US can help differentiate between intrinsic liver diseases and extra-hepatic obstruction. Furthermore, US is more sensitive for detecting stones in the gallbladder.[85]

US can accurately detect dilatation of intrahepatic and extra-hepatic bile ducts, thus providing indirect evidence for the presence of bile duct strictures. However, US is less accurate for determining the etiology and level of obstruction.[86]

Cholangiocarcinoma and PSC may cause biliary obstruction without ductal dilatation, and some benign strictures with partial obstruction may not be associated with biliary dilatation. The sensitivity of US also depends on the degree of obstruction; it has been found to be 94% with a serum bilirubin level of greater than 10 mg/dL but only a sensitivity of 47% with bilirubin levels of less than 10 mg/dL. The sensitivity increases with the serum bilirubin concentration and the duration of jaundice.[87]

B. CT scanning

Spiral CT (SCT) and multidetector CT (MDCT) scanning are highly sensitive for the diagnosis of biliary obstruction, particularly when these modalities are performed with oral and intravenous contrast agents.[88-89))]

Similar to US, CT scanning also helps detect intrahepatic or extra-hepatic bile duct dilatation; however, the main value of CT scanning is its ability to detect the site of obstruction with greater accuracy than US and to help predict the cause of obstruction, especially malignant obstruction. CT scanning is rather insensitive for detecting stones in the CBD.[90].CT cholangiography scanning is another technique that rivals ERCP in delineating biliary tract abnormalities but has not achieved widespread use because of some adverse reactions to the contrast material.[91]

CT scanning is superior to US in visualizing the distal CBD area, because gas artifacts may obscure this region when examined by US. Other important areas that can be seen better on CT scans are the porta hepatis, pancreas, and liver parenchyma.[92]

C. Magnetic resonance imaging (MRI)

Since its introduction, MRCP has rapidly become an important tool for visualizing the biliary system. MRCP takes advantage of the fact that bile has a high signal intensity on T2-weighted images, whereas the surrounding structures do not enhance and can be suppressed during image analysis.[93]

MRCP is as sensitive as US for helping detect cholelithiasis and is superior to US for helping diagnose CBD stones, malignant biliary obstruction, and benign pancreatic disease. Multiple small bile duct stones seen on magnetic resonance cholangiopancreatography (MRCP).[94]The presence of biliary dilatation can be accurately detected by MRCP in 97-100% of patients. The level of obstruction is correct in almost 87% cases.

Bile duct calculi also appear as low signal intensity. CBD strictures and stones can be differentiated as a cause of obstruction in most cases. MRCP is also very useful in helping identify cholangiocarcinoma, which characteristically appears as enhancement in delayed images.More importantly, MRCP provides valuable staging information because of its ability to help visualize the hepatic parenchyma and surrounding vascular structures in the same examination.[95]Benign strictures due to sclerosing cholangitis are multifocal and alternate with slight dilatation or normal-caliber bile ducts, producing a beaded appearance.[96]

Dilatation of both the pancreatic and bile ducts seen using MRCP is highly suggestive of a pancreatic head malignancy. Side-branch ectasia is the most prominent and specific feature of chronic pancreatitis. Thus, MRCP provides a viable alternative to ERCP and allows imaging of the biliary tree when ERCP is unsuccessful; however, MRCP does not currently allow any intervention to be performed, such as stone extraction, stent insertion, or biopsy.[97-98]

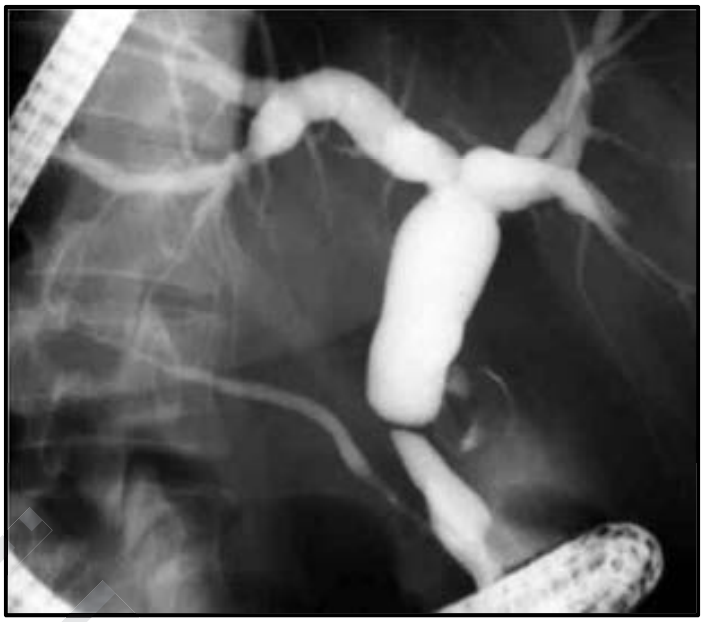

Figure (26): MRCP showing 2 mm long stricture of the common bile duct with prestenotic dilatation. (97)

III. Endoscopy and cholangiography

A. Cholangiography

Cholangiography is generally performed with ERCP but can be performed percutanously (PTC) or intraoperatively (IOC).each route provides both an anatomic view of the bile ducts and functional assessment of whether bile can freely drain through the ducts.(99)

ERCP is a technique using a side-viewing duodenoscope for cannulation of the ampulla of vater and injection of contrast into bile duct.In the diagnosis of Distal biliary tract diseases, ERCP was shown to have sensitivity of 70% versus 84% with MRCP. Evaluation of perihilar biliary obstruction the most common site for cholangiocarcinoma, with both ERCP and MRCP- demonstrated each to be very effective in detecting the presence of obstruction with a sensitivity of 100%. ERCP and EUS remain the best means of diagnosing ampullary cancers due to direct visualization and the ability to biopsy.(100)

The common adverse events with the use of ERCP include pancreatitis with a rate of 1% to 7%, as well as hemorrhage, perforation, and infection. It is therefore recommended that ERCP is reserved for patients with a reasonable likelihood for therapeutic interventions ,for example retrieval of stones and clearance of the duct is successful in more than 90% of cases and in the setting of acute supportive cholangitis can improve the clinical course and be lifesaving. ERCP can also be used for palliation of obstructive lesions in nonsurgical patients or for obtaining tissue for diagnosis as all will be discussed later on.(101)

PTC is also an invasive technique for imaging the biliary system. It requires insertion of needle percutaneously into a dilated bile duct followed by opacification of the bile ducts with an injection of contrast. PTC has close to 100% sensitivity and specificity for identifying the site and the cause of biliary obstruction however; this procedure is invasive and requires sedation. Adverse events rates vary with patient status but include major

adverse events such as sepsis, cholangitis, bile leak, hemorrhage, or pneumothorax at a rate of 2% when a drainage procedure is indicated these rates increases to 2.5 % for sepsis, 2.5% for hemorrhage, 1.2% for infection and 1.7% for death. With the advent of enhanced imaging techniques. PTC should be employed only for patients who warrant therapeutic biliary intervention, but are not candidate for ERCP or who have failed endoscopic biliary access as will be discussed later on.[102]

B. Endoscopic ultrasonography (EUS)

EUS involves the use of echoendoscopes, which have an US transducer mounted at the end of a side-viewing or oblique-viewing endoscope. The linear-array EUS system also has color Doppler capability, enabling the endosonographer to be able to differentiate between vascular and fluid-filled structures. The extra-hepatic bile duct is readily imaged from the duodenum. The instrument also has a small biopsy channel for fine-needle aspiration (FNA) and fine-needle injection.[103]

The pancreas, CBD, and the gallbladder are in close proximity to the distal stomach and the duodenum and can be viewed. EUS can help detect choledocholithiasis, especially small stones, with a sensitivity of more than 95%.[104]

EUS and EUS-guided FNA is a sensitive technique for the diagnosis and staging of cholangiocarcinoma and gallbladder, ampullary, and pancreatic cancer because it can also help detect involvement of regional lymph nodes and vascular invasion by the tumor (an advantage over ERCP in this regard.[105]

EUS is also superior to CT scanning for tumor, node, and metastases (TNM) staging of luminal and pancreatico-biliary malignancies. Porta hepatis lymph nodes are particularly well seen with EUS, in contrast to the relative inability of CT scanning to evaluate the porta region. EUS-guided biliary stenting has become possible with the availability of EUS-guided stents. EUS stenting is performed through the duodenal wall and into the bile duct. In Europe, a dumb bell metal stent is available.[106]

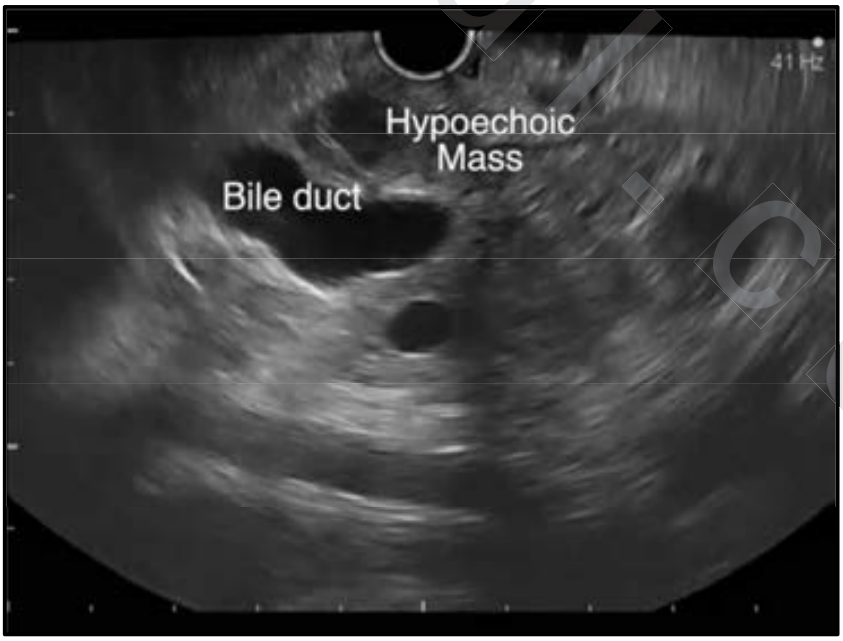

Figure (27): EUS image showing pancreatic mass and dilated CBD.[105]

IV. Pathology

A. Cytology

Cytologic sampling is best performed by brushing the bile duct stricture (biliary stricture) during ERCP or percutaneous transhepatic cholangiography (PTC). Under optimal conditions and using a variety of techniques, cytology sampling can provide a cytologic diagnosis in 75% of cholangiocarcinomas and 50% of pancreatic carcinomas. The results in practice are more disappointing. Routine cytology and histology yield a high specificity but low sensitivity for determining the etiology of bile duct strictures.

Advanced cytologic techniques such as digital image analysis (DIA) and fluorescence in situhybridization (FISH) identify chromosomal abnormalities and improve sensitivity while maintaining high specificity. DIA and FISH enhance the accuracy of standard techniques in evaluation of indeterminate bile duct strictures, allowing the diagnosis of malignancy in a substantial number of patients with false-negative cytology and histology. The sensitivity of FISH could improve the clinical management of patients being evaluated for malignant bile duct strictures by enabling a definitive diagnosis at earlier stages in the clinical evaluation.[107]

Cytologic brushing of bile duct strictures (biliary strictures) is usually performed with wire guidance across the stricture. A plastic brush collects the cytologic specimen from the lining of the bile duct during an ERCP. There is little morbidity associated with brushing of the bile duct. Histologic sampling of a bile duct stricture is performed with an unguided biopsy forceps. This technique is particularly effective for exophytic lesions`.[108]

B. Histologic Findings

Surgically resected segments of the biliary tree will show the etiology of the bile duct stricture. In benign lesions the involved segment of the bile duct is surrounded by a collar of fibrosis causing a narrowing of the lumen. This is accompanied by a variable amount of inflammatory cellular infiltrate comprising a mixture of neutrophils, lymphocytes, plasma cells, and eosinophils.

The mucosa of the strictured segment usually is atrophic, with areas of squamous metaplasia. Periductal onion skin fibrosis seen in primary sclerosing cholangitis. In cholangiocarcinoma, there will be evidence of adenocarcinoma in the cross-sectional histology of the bile duct. In contrast, in autoimmune disease, the hallmark finding is dense lymphocytic infiltration. Periductal lymphocytic and plasma cell infiltrate that is consistent with autoimmune cholangiopathy.[109]

Management

Medical Care

Medical treatment consists of managing complications of bile duct strictures until definitive therapy can be instituted. Most patients who present with cholangitis have a response to antibiotics and supportive management. Patients who are elderly and frail and those presenting with hypotension or altered mental status are best treated in an intensive care unit.[110]

The common organisms that cause cholangitis are Escherichia coli and Klebsiella, Enterococcus, Proteus, Bacteroides and Clostridium species Empiric antibiotic therapy should be effective against these organisms. Traditionally, a combination of a penicillin, aminoglycoside (gentamicin), and metronidazole has been the preferred regimen. Newer penicillins, such as piperacillin/tazobactam or imipenem/cilastatin, also have excellent activity against anaerobes, enterococci, and gram-negative cocci.[111]

Approximately 70-80% of patients' conditions respond to medical therapy and do not need urgent intervention. Patients not having a response to empiric antibiotic therapy within 24 hours or those with hypotension requiring vasopressors, disseminated intravascular coagulation, or multiorgan system failure should be considered for immediate biliary decompression, which can be performed surgically, percutaneous, or endoscopically. Endoscopic or percutaneous decompression is often associated with lower morbidity and should be considered first. Especially preoperatively.[112]

Decompression of the biliary system: preoperative biliary drainage

Percutaneous and endoscopic biliary decompression prior to surgery has been performed for many years. When surgery is delayed, percutaneous or endoscopic drainage of an obstructed biliary system not only relieves the associated symptoms of jaundice (e.g., nausea, pruritis) but also helps to correct the biochemical derangements caused by prolonged biliary obstruction. Preoperative drainage allows time for surgical planning, detailed imaging, and proper laboratory testing. Correction of nutritional and biochemical derangements prior to surgery may result in improved surgical outcomes.[113]

Operative treatment

Surgical management of benign bile duct strictures is necessary for patients with a low surgical risk in whom endoscopic therapy has failed. Surgical management consists of restoration of biliary enteric continuity, which usually is achieved with a defunctionalized Roux-en-Y jejunal loop by means of hepaticojejunostomy, choledochojejunostomy, or intrahepatic cholangiojejunostomy. Patients with long-standing benign bile duct strictures (biliary strictures) due to pancreatitis may require pancreaticoduodenectomy. However, surgical drainage has been associated with considerable morbidity and mortality.[114]

Surgical therapy of malignant bile duct strictures (biliary strictures) consists of either attempting a curative resection of the tumor or performing a palliative operation. Careful staging of the tumor should be performed in order to select patients who are likely to have surgically resectable disease. Surgical intervention is recommended for those patients who are otherwise healthy, whose disease appears to be localized, or in whom duodenal or gastric outlet obstruction is present.[115]

Role of ERCP in management of distal CBD strictures

Background

Endoscopic retrograde cholangiopancreatography (ERCP) is a technique that uses a combination of luminal endoscopy and fluoroscopic imaging to diagnose and treat conditions associated with the pancreatobiliary system. The endoscopic portion of the examination uses a side-viewing duodenoscope that is passed through the esophagus and stomach and into the second portion of the duodenum. With the scope in this position, the major duodenal papilla is identified and inspected for abnormalities. This structure is a

protrusion of the hepatopancreatic ampulla (also known as the ampulla of Vater) into the duodenal lumen. The ampulla is the convergence point of the ventral pancreatic duct and common bile duct (CBD) and thus acts as a conduit for drainage of bile and pancreatic secretions into the duodenum.[116]

The minor duodenal papilla is also located in the second portion of the duodenum and serves as the access point for the dorsal pancreatic duct. Evaluation of the dorsal pancreatic duct with ERCP is rarely performed. After the papilla has been examined with the side-viewing endoscope, selective cannulation of either the CBD or the ventral pancreatic duct is performed. Once the chosen duct is cannulated, either a cholangiogram (CBD) or a pancreatogram (pancreatic duct) is obtained fluoroscopically after injection of radiopaque contrast material into the duct. [117]

ERCP is now primarily a therapeutic procedure; thus, abnormalities that are visualized fluoroscopically can typically be addressed by means of specialized accessories passed through the endoscope. Because ERCP is an advanced technique, it is associated with a higher frequency of serious complications than other endoscopic procedures are. Accordingly, specialized training and equipment are required, and the procedure should be reserved for appropriate indications.[118]

Indications

Since its first description in the late 1960s as a diagnostic technique. ERCP has evolved into an almost exclusively therapeutic procedure. The main reason for this evolution is that diagnostic modalities have been developed that are less invasive than ERCP but possess similar sensitivity and specificity for disease processes of the hepatobiliary system.[119]

Because ERCP has a higher rate of severe complications than most other endoscopic procedures do, having an appropriate indication for its use is extremely important. In fact, most ERCP-related legal claims center on the aptness of the indication for the procedure. The American Society for Gastrointestinal Endoscopy (ASGE) has published guidelines regarding the role of ERCP in biliary tract and pancreatic diseases. The indications contained in these guidelines, divided according to organ system, may be summarized as follows.[120]

1. Indications for biliary disease include the following:[119-120]

- Assessment and treatment of biliary obstruction secondary to choledocholithiasis - Precholecystectomy ERCP may be indicated when persistent or worsening jaundice, persistent or worsening pancreatitis, or cholangitis is present.
- Treatment of choledocholithiasis identified during cholecystectomy with intraoperative cholangiography or CBD exploration without stone extraction.
- Assessment and treatment of bile duct strictures - Malignant strictures, benign strictures, congenital bile duct abnormalities.
- Assessment and treatment of postoperative biliary leaks.
- Assessment and treatment of selected patients with sphincter of Oddi dysfunction.

2. Indications for pancreatic disease include the following:

- Assessment and possible treatment in patients with an unknown underlying cause of recurrent, acute pancreatitis.
- Assessment and treatment of symptomatic strictures associated with chronic pancreatitis.

- Assessment and treatment of symptomatic pancreatic duct stones.
- Assessment and treatment of pancreatic duct disruptions or leaks.
- Treatment of symptomatic pancreatic pseudocysts or benign pancreatic fluid collections.

3. Indications for diagnosis of pancreatic malignancies include the following:

- Pancreatoscopy.
- Bile duct brushing and biopsy.
- Intraductal ultrasonography.

4. Indications for ampullary disease include the following:

- Assessment and treatment of ampullary adenomas.
- Assessment of ampullary malignancy.

Contraindications

- Absolute contraindications for ERCP includes:
  1. Patient refusal to undergo the procedure;
  2. Unstable cardiopulmonary, neurologic, or cardiovascular status;
  3. Existing bowel perforation.
- Relative contraindications for ERCP includes:
  1. Structural abnormalities of the esophagus, stomach, or small intestine such as esophageal stricture, Para esophageal herniation, esophageal diverticulum, gastric volvulus, gastric outlet obstruction, and small bowel obstruction
  2. An altered surgical anatomy, such as is seen after partial gastrectomy with Billroth II or Roux-en-Y jejunostomy.
  3. The presence of acute pancreatitis is typically considered a relative contraindication as well, unless the etiology of the pancreatitis is gallstone-related and the therapeutic goal is to improve the clinical course by means of stone extraction.

In addition, ERCP with sphincterotomy or ampullectomy is relatively contraindicated in coagulopathy patients

Technical considerations

Attention to proper procedure and technique will optimize results and minimize complications

I. Best practices

The following measures will improve the performance of ERCP:

- Before ERCP, all of the patient's previous abdominal imaging findings (from CT scans, magnetic resonance imaging [MRI], ultrasonography, and cholangiography or pancreatography) should be reviewed; this can facilitate location of the pathology during ERCP, as well as help pinpoint any changes that occurred since the previous imaging was performed.[121]
- A scout radiograph should be obtained while the patient is on the fluoroscopy table and before insertion of the duodenoscope; this image can act as a baseline for comparison with subsequent fluoroscopic images taken after contrast injection.[122]
- The patient's surgical history should be reviewed before the procedure to determine whether there is anything in the surgical anatomy that may be a contraindication for

ERCP. To minimize the patient's exposure to radiation, fluoroscopic images should be obtained only as necessary during the procedure; some fluoroscopy machines can be adjusted to minimize the frequency of image acquisition.[123]

- Deep sedation is desirable during ERCP because a stable endoscopic position in the duodenum is important for proper cannulation, therapeutic intervention, and avoidance of complications. If the pancreatic duct is cannulated several times or if contrast is injected into the pancreatic duct, placement of a temporary pancreatic duct stent should be considered in order to decrease the risk of post-ERCP pancreatitis.[124]

II. Equipment

Materials required for endoscopic retrograde cholangiopancreatography (ERCP) include an endoscope, image processing equipment, cannulation devices, therapeutic accessories, and protective gear.

1. Endoscope (side- or forward-viewing)

The standard endoscope for ERCP is the therapeutic side-viewing duodenoscope, which has a side-viewing objective lens, a tip with 4-way angulation capability, a side-positioned air/water nozzle, a 4.2-mm instrument channel, and a forceps elevator adjacent to the instrument channel outlet that allows fine linear instrument position changes. In certain situations where a traditional duodenoscope is not suitable (e.g., in patients with a Billroth II or a Roux-en-Y reconstruction), a forward-viewing endoscope may be tried instead.[125]

2. Image processing equipment

Appropriate endoscopic video processing equipment is needed in a procedure room that can also accommodate fluoroscopy. Most centers have a dedicated procedure room that incorporates either a permanent fluoroscopy table or a portable C-arm device, along with the video processing equipment specific to a particular brand of endoscope. Dual video monitors or split-screen capability must be available in the endoscopist's direct field of view; simultaneous fluoroscopic and endoscopic imaging is required for proper completion of ERCP.[126]

Fluoroscopic imaging in ERCP requires the injection of a radiopaque marker into either the biliary tree (cholangiography) or the pancreatic duct (pancreatography). Iodinated contrast agents are most commonly used, though non-iodinated agents are also available.

Undiluted contrast is appropriate for initial fluoroscopic images or when fine imaging details are desired (as in visualizing the pancreatic duct). Half-strength contrast is preferable for certain purposes, such as assessment for choledocholithiasis in a dilated bile duct. Because of concerns over systemic uptake of iodinated contrast agents during ERCP, prophylactic steroid and diphenhydramine therapy before contrast administration is a common practice in patients with a history of hypersensitivity to such agents. Although prophylactic medication and substitution of non-iodinated contrast are reasonable.[127]

3. Cannulation devices

Most endoscopists have adopted the sphincterotome as their primary cannulation device for ERCP, primarily because this device has the ability to cannulate both the biliary and pancreatic ductal system, as well as perform sphincterotomy, without having to be switched out. Most currently available sphincterotomes have multiple lumens that allow the passage of a guide wire or injection of contrast.

Current sphincterotomes also have a cutting wire of varying length that both allows coagulative cutting and has the ability to alter the curvature of the radiopaque tip of the device. Tension can be applied to the cutting wire via an operator-controlled handle, which causes the tip of the sphincterotome to bow; this ability to bow and unbow the tip of the device can facilitate cannulation and cutting. Different tip diameters and degrees of taper are also available, depending on the clinical situation.[128]

Once the sphincterotome is in the proper position, most endoscopists use a wire-guided approach to cannulation, in which a guide wire is passed through one of the sphincterotome lumens and into either the common bile duct (CBD) or the pancreatic duct before contrast injection. This approach not only facilitates acquisition of ductal access but also allows accessories to be more safely passed into the ductal system over the wire.

Many different guide wires are available from several different manufacturers. They vary with respect to diameter (0.02-0.035 mm), degree of rigidity, outer coating material, tip angle, and even bending or coiling tendency with the application of pressure. By taking these characteristics into account, one can readily choose the appropriate wire for a specific situation.[129]

The cannulation catheter is a more traditional tool, which some endoscopists still prefer to the sphincterotome. A cannulation catheter is similar to a sphincterotome in that it often contains multiple lumens for contrast injection or wire passage and a radiopaque tip. It differs from a sphincterotome in that it has no cutting wire but can include a specialized tip (e.g., a ball tip or needle tip) that can facilitate passage of the catheter into a duct with a particular structural property.[130]

4. Therapeutic accessories

Once access to either the biliary or the pancreatic ductal system is gained, various accessories can be passed over the wire for use in therapeutic interventions. These accessories include tools that are specific to a certain indication, such as stone extraction balloons or baskets, stricture dilating balloons or catheters stents of various types, cytopathology brushes, and even cholangioscopes for intraductal visualization.[131]

5. Protective gear

All personnel within the ERCP procedural area should be protected from the scattered radiation produced by the fluoroscopy unit. Standard protective apparel includes a lead apron and a thyroid shield with a lead thickness of 0.2-0.5 mm. Two-piece lead apparel in the form of a skirt and vest is also available, depending on the wearer's preference. The use of leaded radiation safety glasses is also advocated; repeated radiation exposure to the eye can be hazardous. Additional protective gear recommended for use during ERCP includes a face shield, surgical gloves and gown, and shoe covers if desired.[132]

III. Patient preparation

Several different choices of anesthetic approach are available. Insertion of a side-viewing duodenoscope can be somewhat difficult, given the lack of a forward-viewing lens; thus, proper patient and endoscope positioning are crucial for safe passage down the esophagus.

1. Positioning

The prone position is standard for ERCP because it offers the best access for anterior-posterior fluoroscopic imaging.[133]

A. ***Semi-prone position***

Some endoscopists prefer the semi-prone position. Although this pose may not yield optimal image quality, it may be preferable for certain patients (e.g., those who are obese or have respiratory compromise). Some endoscopists also find it easier to pass the duodenoscope into the small bowel while the patient is in this position.

B. The supine position

Indications for the use of this position include endoscopist preference, comorbid conditions, pregnancy, and any factor that necessitates closer airway monitoring during the procedure.

2. Approach considerations

The main objectives of endoscopic retrograde cholangiopancreatography (ERCP) are to gain access to the biliary system or the pancreatic duct via the major duodenal papilla in the second portion of the duodenum, to obtain fluoroscopic images of either the biliary tree or the pancreatic duct after injection of a radiopaque contrast agent, to interpret those images in real time, and to perform therapeutic intervention if indicated.[134]

IV. Steps in procedure

The main steps of ERCP are as follows.

1. Insertion of endoscope

With the patient in the prone or semi-prone position, the duodenoscope is passed through a self-retaining mouth guard with the tip angled slightly downward to facilitate its movement to the level of the hypo-pharynx.

Once the endoscope has reached this location, the tip is brought back to the neutral position, and gentle pressure is applied until passage into the proximal esophagus is achieved. Care must be taken in passing the endoscope through the esophagus and into the stomach; visibility is limited. If attempts to pass the duodenoscope meet with resistance and no cause is visible, removal of the duodenoscope and subsequent examination with a gastroscope should be considered.[135]

2. Gastric examination and duodenal positioning

Once the duodenoscope is in the gastric lumen, it is advanced to a position in which it lies on the mucosa of the greater curvature, allowing visualization of the lesser curvature and the distal stomach.

With further advancement of the endoscope, the tip should pass the angular incisure. In this position, upward angulation of the tip should allow examination of the gastric cardia.

In the distal stomach, downward angulation of the tip should bring the pylorus into view. When the endoscope reaches the pylorus, the tip should again be placed in the neutral position, with the pylorus visible in the 6-o'clock location as passage into the duodenal bulb is achieved.

The duodenoscope is advanced to the distal aspect of the first portion of the duodenum, and the tip is angled to the right and slightly upward. The scope is then carefully withdrawn and slight clockwise torque applied to bring the endoscope into the "short position." This maneuver should advance the endoscope to the second portion of the duodenum and permit visualization of the major duodenal papilla, which appears as a small, pink-colored protuberance at the junction of the horizontal and vertical duodenal folds.[136]

3. Cannulation of major papilla

The key to successful cannulation of either the pancreatic or the biliary ductal system is proper scope positioning. With the duodenoscope in the short position in the second portion of the duodenum, the lens should be facing the papilla, with the tip in close proximity to the duodenal wall. For easier cannulation of the common bile duct (CBD), the scope should be positioned so that the image of the papilla is in the upper portion of the video monitor; this allows an upward approach to the papilla, which is more in line with the natural path of the CBD. In contrast, cannulation of the pancreatic duct is more easily achieved via an approach that is more perpendicular to the duodenal wall.[137]

If possible, the intraduodenal segment of the CBD should be observed before the initial attempt at cannulation so that the duodenoscope can be lined up with the natural contour of the bile duct. As a rule of thumb, for cannulation of the CBD, the cannulation device should be aimed in a slightly tangential direction to the 10-11 o'clock position; for cannulation of the pancreatic duct, the device should be pointed to the 1-o'clock position.

The traditional approach to cannulation, termed contrast-guided cannulation, involves passage of the cannulation device tip into the papillary orifice, followed by injection of contrast material to confirm proper positioning. However, there are now data to support a wire-guided approach. In the wire-guided approach, a guide wire is passed under fluoroscopy into either the pancreatic duct or the CBD before the injection of contrast.[138]

Several anatomical abnormalities may make cannulation of the bile duct more challenging. The most common of these anomalies, the presence of a periampullary diverticulum, occurs in approximately 7.5% of patients undergoing ERCP for any indication. Although the ampulla is typically adjacent to the rim of a diverticulum or between 2 diverticula, it may also be found inside the diverticular sac.[139]

When the ampulla is located outside the diverticulum, the natural course of the CBD is often unaltered; however, when it is located inside the sac, this may not be the case, and proper alignment of the duodenoscope can be extremely difficult. In view of the risk of bowel perforation, considerable care should be taken in repositioning the duodenoscope in the presence of a diverticulum.

Another scenario that may make cannulation of the major papilla difficult is the presence of a distal ductal defect, such as an impacted biliary stone, a distal bile duct tumor or stenosis, or a pancreatic head mass. A wire-guided approach to cannulation is typically recommended in these circumstances. Cannulation with guide wires of varying diameter or stiffness may be necessary for successful entry into the system, depending on the clinical scenario.[140]

4. Cannulation of minor papilla

Occasionally, cannulation of the minor papilla is desired to search for a possible anatomic anomaly (e.g., pancreas divisum) or to perform a minor duct sphincterotomy in a symptomatic patient with known pancreas divisum.

Pancreas divisum is a congenital anatomic variant in which the ventral and dorsal pancreatic ducts fail to fuse. Although most patients with this variant are asymptomatic, a small subset of patients with pancreas divisum may present with recurrent acute pancreatitis. In these symptomatic patients, minor duct sphincterotomy may be beneficial (after other common causes of acute pancreatitis have been ruled out).[141]

The minor papilla is generally located about 1-2 cm proximal to the major papilla in the second portion of the duodenum. It typically looks like a smaller version of the major papilla but may be difficult to visualize in some patients. It can be located by first visualizing the major papilla and then slowly withdrawing the scope while looking slightly to the right. Cannulation of the minor duct usually requires a smaller cannulating device (e.g., a cannulation catheter with a needle tip) and the use of a wire-guided approach before contrast injection.(142)

5. Fluoroscopic imaging

Once passage of a guide wire into either the CBD or the pancreatic duct has been confirmed by means of fluoroscopy, the cannulation device is advanced into the duct, and a radiopaque contrast agent is injected.

With the patient in the prone, semi-prone, or supine position either on a dedicated fluoroscopy table or under a portable C-arm device, a cholangiogram or a pancreatogram is obtained by the endoscopist. This measure allows immediate assessment for ductal structural abnormalities or filling defects, from stones. If intervention is required, accessories can be passed over the guide wire into the duct with the help of fluoroscopy. Fluoroscopic imaging is also typically performed after intervention to assess the adequacy of the treatment (e.g., to look for residual filling defects in a bile duct after stone extraction).(143)

6. Therapeutic intervention

Most patients who present for ERCP have previously undergone noninvasive diagnostic testing (e.g., computed tomography [CT], magnetic resonance cholangiopancreatography [MRCP], or ultrasonography) that revealed an abnormality potentially amenable to intervention via ERCP.

Thus, cholangiography, pancreatography, or both are performed to confirm or to better characterize a potential lesion and are followed by an intervention if treatment is indicated. Although a multitude of therapeutic ERCP maneuvers are known, the most common are those dealing with biliary or pancreatic duct stones, malignant or benign strictures or stenosis, leaks, and tissue sampling.(144)

A. Biliary sphincterotomy

For example, to manage choledocholithiasis, a biliary sphincterotomy is generally performed initially to facilitate passage of the stone through the distal bile duct. Once this is done, devices such as a stone extraction balloon or a stone basket (with or without stone crushing capacity) can be passed over the guide wire in the bile duct to help deliver the stone. If this approach is unsuccessful, more advanced accessories (e.g., electrohydraulic or laser lithotripsy devices) can be used.(145)

B. Stent insertion

Another common intervention involves placing a biliary stent into the bile duct to treat a biliary obstruction secondary to benign or malignant biliary stricture Multiple stents are available, varying in design, material, and size; the choice of an appropriate stent depends on the clinical situation.(146)

Types of biliary endoprostheses and stent survival

1. Plastic Stents

Typical materials used in the composition of plastic stents include Teflon, Percufex, polyethylene, and polyurethane. Plastic stents are prone to early occlusion secondary to bacterial colonization and development of a bio-film over their internal surface.[147]

An increase in stent diameter of 0.2 mm results in a three-fold increase in the rate of bile flow, and so, If one presumes the reverse to be true, the decreased rate of bile flow secondary to stent narrowing further encourages precipitation of bile salts.[148]

The composition of the bile draining through the stent may also be a factor; sludge within bile increases its viscosity and causes early stent failure in up to 30% of plastic stents.[149]

Plant fibers from duodenal reflux may also become incorporated into the intraluminal precipitation and further contribute to stent clogging. Microscopic irregularities on the internal surfaces of stents have been shown to enhance precipitation, and attempts have been made to develop coatings which impede colonization by bacteria.[150]

These include hydrophilic polymer-coated polyurethane stents, silver-coated stents, and linings bonded with antimicrobial agents however, data regarding the clinical efficacy of such modifications are lacking. In addition, the use of systemic prophylactic antibiotics has also been postulated as a method of prolonging stent patency. [151]

In vitro studies have demonstrated that quinolones such as ciprofloxacin are able to achieve high concentrations within bile and reduce bacterial adhesion. Systemic antibiotic prophylaxis has been combined with ursodeoxycholic acid (USD) in a further attempt to prolong patency rates of plastic stents. USD is a bile-modifying agent, used in the treatment of primary biliary cirrhosis and occasionally indicated in the treatment of cholesterol-predominant gallstones.[152-153]

Since disruption of the sphincter of Oddi (by passage of a stent across it) allows the ascent of micro-organisms (with subsequent colonization of the endoprosthesis), it may be feasible to reduce bacterial colonization by positioning stents above the sphincter, thus allowing it to function normally.[154-155]

The only factor that has been consistently shown to reduce encrustation and prolong patency of plastic stents is its internal diameter.[156-157] The typical size of plastic stents varies from 7 Fr to 10 Fr;[158-159] however, stents of up to 14 Fr may be employed. The insertion of these stents is limited by the trauma of insertion and discomfort when positioned endoscopically.

A further consideration is that there are few duodenoscopes that can accept stents over 12 Fr in diameter. When a radiologic route is used, the larger track size required trans-hepatically may significantly increase the risk of bleeding and bile leak after insertion. The risk of stent occlusion increases over the period of time following insertion.

For this reason, many centers employing plastic stents as palliation will undertake routine stent changes at intervals of 3 months or greater. Stent migration can also be a problem, but it appears to be more common when used for benign biliary disease with a concomitant sphincterotomy.

The use of multiple stents has been previously described for benign biliary conditions but not for malignant strictures (other than hilar strictures).[160-161] Having additional stents in situ increases the functional diameter for biliary drainage and may also allow free drainage of bile from around the stents, should one occlude.

2. Metal Stents

Patency rates of plastic stents fueled the development of metal stents which are self-expanding, allowing their deployment over a narrow track if done percutaneously, or via standard delivery systems if positioned endoscopically.

The internal diameter of a metallic stent when fully expanded can be up to three-times greater than that of a standard plastic prosthesis. Other purported advantages are that metal stents become covered by biliary epithelial cells and so are incorporated into the bile wall, reducing the risk of migration. But also precluding their use for benign conditions.

The spaces between the supporting struts of metal stents allow further drainage of bile between them. This feature may be of particular value in allowing bilateral decompression of the biliary tree when stents are utilized for hilar strictures.[162]

The main thrust behind the evolution of metal stents is the larger internal diameter, which should, in theory, increase long-term patency rates. There are several designs of metallic stents, with variations in diameter of the expanded stent (10 mm to12 mm), the diameter of their delivery system (7 Fr to12 Fr) length of stent, and wall thickness. The most common type in use is the Wall stent, made of cobalt alloy with a fully expanded diameter of 30 Fr and delivery systems of 7 Fr.[163]

The major drawback to the use of metallic stents is their price, metallic stents being 15-40 times dearer than plastic stents.[164] It can be argued that greater initial 'outlay' costs are made up for by longer survival, greater patency rates, and reduced need for intervention

3. Covered metal stents

Whilst displaying a possible greater resistance to early occlusion than plastic stents, metallic stents can still become blocked, the mechanism for this being tumor ingrowth around and into the spaces between the metal lattice in the stent side-wall. In an attempt to counteract this problem silicone-lined stents have been designed to occlude the interstrut spaces.

In a further advance on this, covered stents with linings bounded to cytotoxic agents, such as paclitaxel, are also now available for clinical use, although there are no significant data regarding their efficacy in humans.(One may summarize that potential advantages gained in longer patency from such covered stents may only be fully realized for distal malignant strictures, since the loss of inter-strutspaces may impede drainage of hilar lesions.[165]

4. Treating Stent Occlusion:

Plastic stent occlusion, when it does occur, is relatively easily treated by repeat endoscopy and re-insertion of another metallic/plastic stent. If an endoscopic approach is no longer possible, due to duodenal compression from an advanced malignancy, then a percutaneous insertion of the stent can be employed.

Occlusion of metal stents can be more problematic, since the stent cannot easily be removed after insertion and the unblocking of such stents usually requires the reestablishment of a lumen with the blocked stent in situ.

Techniques described include balloon trawling of the stent endoscopically[166], and insertion of a plastic endoprosthesis or re-insertion of a second metallic stent thought the lumen of the occluded stent.[167-168] Of these methods, it has been reported that reinsertion of a further restent, in particular a metal stent, offers the best chance of successful re-canalization.[169]

5. Stent-related complications

Irrespective of the techniques employed to deploy biliary endoprosthesis, the stents themselves may also cause complications and contribute to post-procedure morbidity.

Plastic stents have been reported to cause duodenal perforation by being incorrectly placed at the time of procedure, with the result that the mechanical force exerted by the tip of the plastic stent against duodenal intestinal mucosa causes necrosis over time.

Inflexibility or a stent of an incorrect length may also lead to pressure necrosis[170-171] Perforations may also occur secondary to stent migration. Case reports exist of stents causing colovaginal fistulae,[172] colovesical fistulae,[172] colocutaneous fistulae,[173] perforations within parastomal hernia, [174] or other incarcerated herniae,[175] perforations of sigmoid diverticulae,[176] and small bowel perforations, usually involving the distal ileum.[177-178] In many of these cases, stent perforation occurs within the presence of other, unrelated, bowel abnormalities, including colonic diverticulae and abdominal wall herniae. Although the migration of metallic stents is less common, it may still occur in up to 6% of cases.[179]

Stent fracture has been reported,[179] and acute pancreatitis, duodenal perforation, upper gastrointestinal bleeding,[180] and even air embolism,[181] have been reported following metallic stent deployment

C. Stricture dilation

1. <u>Benign strictures</u>

- Benign biliary strictures may be dilated with hydrostatic balloons or a graduated catheter passed over a guide wire. Indications for endoscopic dilation of benign strictures include postoperative strictures, dominant strictures in sclerosing cholangitis, chronic pancreatitis, and stomal narrowing after choledochoenterostomy.[182]
- Stent placement may be used to maintain patency after initial dilation when using single or multiple endoscopic prostheses. Serial endoscopic dilations and stent placement can be used to achieve prolonged ductal patency in benign strictures secondary to chronic pancreatitis and postoperative strictures.[183]
- Although early results with this technique in patients with biliary strictures secondary to chronic pancreatitis are encouraging, long-term results tend to be Poor.
- In addition, in the subgroup of patients with calcification of the pancreatic head, outcomes were even worse, Placement of multiple plastic stents to dilate and to treat chronic biliary strictures caused by chronic pancreatitis is a viable option but has been associated with rare cases of death from biliary sepsis.[184]

- In addition, even patients with successful biliary stricture dilation via stents have a restenosis rate after stent removal of up to 17%.The use of multiple stents exchanged every 3 months over a longer time period (up to 14 months) may be more efficacious than single stents for treatment of biliary strictures caused by chronic pancreatitis.[185]
- Strictures that develop in patients with primary sclerosing cholangitis (PSC) tend to respond well to endoscopic therapy, either with balloon dilation alone or in combination with the placement of endoscopic stents. The limited data available on this topic suggest that balloon dilation may be sufficient and that the use of stents to treat these strictures may be associated with an increased risk of complications and cholangitis.
- Endoscopic therapy of strictures has been shown to be beneficial overall in patients with PSC, and one study suggested that it may improve survival.[186]
- Although endoscopic therapy in PSC has not been shown to delay liver transplantation or to allow early identification of cholangiocarcinoma, cholangiograms obtained at ERCP have been shown to have some prognostic value when combined with other patient-derived factors. Dominant strictures seen in patients with PSC should undergo endoscopic brushing and biopsy to assess for the presence of malignancy.[187]
- With regard to benign postoperative bile-duct strictures, outcomes via treatment with balloon dilation and stents are encouraging but far from optimal, and clinical success rates with these modalities can range from 55% to 8%.[188]

2. <u>Malignant strictures</u>

- Dilation of malignant strictures may occasionally be necessary before stent insertion. The role of preoperative biliary decompression for malignant obstruction because of pancreatic cancer should be limited to those patients with acute cholangitis or those who have severe pruritus and a delay in surgical resection.[189]
- Large-caliber polyethylene stents are used most commonly. In expert hands, stent placement is successful in 90% of distal bile-duct strictures occurring in the setting of pancreatic, ampullary, and distal bile-duct cancers. [190]
- For proximal (Klatskin) lesions, success rates are lower, biliary drainage may be incomplete, and the incidence of early cholangitis is higher. Such tumors may require the placement of stents into both right and left hepatic ducts to achieve adequate drainage. Minimal contrast injection and the use of preprocedural imaging studies to direct unilateral drainage of patients with hilar tumors may decrease the rate of cholangitis.[191]

V-Complications of procedure

- ERCP is an advanced endoscopic technique that carries a higher risk of procedure-related complications than other endoscopic procedures do.
- Besides the risks associated with most other endoscopic procedures (eg, mucosal perforation related to traumatic passage of the endoscope, cardiopulmonary events, adverse intravenous medication reactions, hemorrhage, infection, or oxygen desaturation), ERCP also carries a risk for the following specific complications[192]:
- Post-ERCP pancreatitis.
- Postsphincterotomy bleeding.
- Infection (cholangitis, bacteremia).
- Retroperitoneal perforation.

V. Early complications

- Early complications develop in approximately 5% of patients after attempted endoscopic biliary stenting and are not related to the type of stent used.
- Early complications were reported in patients with malignant CBD obstruction as follows: biliary infection (35 %), pancreatitis (29 %), bleeding (23 %), perforation (6 %), early stent migration and renal failure (3% each).[193]
- Post-ERCP biliary infection is a serious complication that is fatal in 8%–20% of cases and is best prevented by complete biliary drainage.[53,65] Recent guidelines recommend routine antibiotic prophylaxis in selected patients (with liver transplant, or severe neutropenia, advanced hematological malignancy, or anticipated incomplete biliary drainage) and a full antibiotic course if adequate biliary drainage is not achieved during the procedure.[193]
- Post-ERCP pancreatitis is usually mild but it may rarely be fatal. Recent ESGE guidelines recommended periprocedural rectal administration of non-steroidal anti-inflammatory drugs for procedures at low risk of post-ERCP pancreatitis and consideration of prophylactic pancreatic stent placement in high risk conditions, including precut biliary sphincterotomy, pancreatic guide wire assisted biliary cannulation and simultaneous presence of several risk factors for post-ERCP pancreatitis. These measures have not yet been largely adopted in the endoscopy community.[194]
- Bleeding is associated with sphincterotomy, not with biliary stenting[69]; it is made more likely by coagulation disorders but not by aspirin or by nonsteroidal anti-inflammatory drugs. sphincterotomy is envisaged, patients with a clinical history suggestive of a bleeding disorder (as is frequently the case in patients subjected to biliary stenting) should undergo testing of platelet count and prothrombin time .these parameters should be managed to obtain adequate values during sphincterotomy, and blended current should be used.[195]

VI. Complication prevention:

- Procedure-specific risk factors for post-ERCP pancreatitis include difficult cannulation of the ampulla of Vater (> 10 attempts), cannulation of the pancreas duct, injection of contrast into the pancreas duct, pancreatic duct sphincterotomy, and precut sphincterotomy. The use of prophylactic pancreatic duct stents in patients who are at increased risk for pancreatitis is recommended because it has been shown to reduce the incidence of post-ERCP pancreatitis in this cohort of patients.[196]
- Those at higher risk for post-ERCP hemorrhage include patients with either a pathologic or an iatrogenic coagulopathy. Anticoagulant therapy should be discontinued before elective ERCP (generally 5 days beforehand), and the prothrombin time (PT) and partial thromboplastin time (PTT) should be evaluated on the day of the procedure. If the PT and PTT are significantly abnormal, the procedure should be rescheduled if it is not an emergency. If there is an urgent need for ERCP, reversal of the coagulopathy with fresh frozen plasma may be required.[197]
- Routine use of prophylactic antibiotics in elective ERCP is controversial. The infectious risks of ERCP (e.g., bacteremia and cholangitis) are most likely to occur in patients who present with biliary obstruction. Current guidelines recommend prophylactic antibiotic therapy in all patients presenting with biliary obstruction and cholangitis or with biliary

obstruction that is unlikely to be drained at the time of ERCP. Antibiotic therapy is also recommended after any unsuccessful ERCP biliary drainage procedure.[198]

- Most mucosal perforations occurring during ERCP are periampullary and are associated with sphincterotomy. Periampullary perforations are usually retroperitoneal and can often be managed with supportive care rather than immediate surgical intervention. This complication can be prevented in many cases by following proper landmarks while performing sphincterotomy and by taking care to not cut beyond the intraduodenal portion of the CBD.[199]
- Perforations occurring away from the ampulla are typically due to traumatic endoscope passage, often related to limited visualization of the lumen. As a general rule, the duodenoscope should never be forced against significant resistance during insertion. The forceps elevator should be in the closed position during passage of the endoscope down the lumen because it may lacerate the adjacent tissue if left in the open position.[200]

VII. Expected outcomes

Because of inherent bias and patient underreporting, an accurate estimate of the procedural complication rate is difficult to obtain. However, comparisons with complication data pertaining to other endoscopic procedures makes it clear that ERCP is associated with approximately 4-fold higher rates of severe complications.

Role of PTC in management of distal CBD stricture

I. Definitions

1. Percutaneous trans-hepatic cholangiography: is a diagnostic procedure that involves the sterile placement of a small gauge needle into peripheral biliary radicles with use of imaging guidance, followed by contrast material injection to delineate biliary anatomy and potential biliary pathologic processes. The findings are documented on radiographs obtained in multiple projections.[201]
2. Percutaneous trans-hepatic biliary drainage: is a therapeutic procedure that includes the sterile cannulation of a peripheral biliary radicle after percutaneous puncture followed by imaging-guided wire and catheter manipulation. Placement of a tube or stent for external and/or internal drainage completes the procedure. Percutaneous therapy of biliary lesions is often staged, requiring several sessions to achieve the therapeutic goals. Percutaneous cholecystostomy is a therapeutic procedure that involves the sterile placement of a needle into the gallbladder with use of imaging guidance to aspirate bile.[202-203]
3. Successful percutaneous trans-hepatic cholangiography: is defined as sufficient needle localization and contrast material opacification to allow image-based diagnosis or planning of treatment.[204]
4. Successful biliary drainage: is defined as the placement of a tube or stent with use of imaging guidance to provide continuous drainage of bile.[205]

II. Indication

Percutaneous Trans-hepatic Cholangiography: indication[206]

- Define level of obstruction in patients with dilated bile ducts.
- Evaluate for presence of suspected bile duct stones.
- Determine etiology of cholangitis.
- Evaluate suspected bile duct inflammatory disorders.
- Demonstrate site of bile duct leak.
- Determine etiology of transplanted hepatic graft dysfunction

Percutaneous trans-hepatic biliary drainage: indications[207]

- Provide adequate biliary drainage.
- Decompress obstructed biliary tree.
- Divert bile from and place stent in bile duct defect.
- Provide a portal of access to the biliary tract for therapeutic purposes that include but are not limited to Dilatation of biliary strictures.
- Remove bile duct stones.
- Stent malignant lesions.
- Brachytherapy/phototherapy.
- Endoluminal tissue sample or foreign body retrieval.

III. Steps

- Opacification of the biliary system was first reported in 1921 with direct puncture of the gallbladder. Subsequent reports described direct percutaneous biliary puncture. The technique was revolutionized in 1960s with the introduction of fine-gauge (22- to 23-gauge) needles. Since the 1960s, PTC has been used for the diagnosis and treatment of biliary tract disorder.[208-209]
- The technique consists of introducing a 22- or 23-gauge needle through the skin in the right ninth or tenth intercostal space in the midaxillary line and advancing into the liver parenchyma under fluoroscopic guidance. Contrast material is injected while the needle is slowly withdrawn, until the bile ducts are opacified and thus provide a portal of access to the biliary tract for mid- to long-term diagnostic purposes.
- Cholangiography from an indwelling percutaneous biliary drain site is probably a lower-risk cholangiography procedure than repetitive de novo percutaneous trans-hepatic cholangiography with the use of needles.[210]
- Many cases, percutaneous trans-hepatic cholangiography (PTC) is followed by the placement of percutaneous biliary catheters for drainage. Percutaneous biliary drainage (PBD) is needed in many patients. For example, it may be helpful in relieving obstructive symptoms, especially those due to unresectable malignant tumors (as s as well as in treating those with various types of benign strictures (including postoperative strictures), primary sclerosing cholangitis and liver transplants.[211-212]
- Once the needle is in the bile duct, a 0.018-inch wire is advanced. After the wire is passed to a secure position in the biliary tree, the needle is removed. For further interventions, a larger (e.g., 0.035- or 0.038-inch) wire is needed. A sheath of the coaxial system can be passed over the 0.018-in. wire, and the inner 2 components (wire and inner coaxial dilator) can then be removed to accept the larger wire.[213-214]

- The assembly set,: consisting of an outer fluoropolymer sheath (Teflon; DuPont, Wilmington, Del), inner fluoropolymer sheath (Teflon; DuPont), and a metal cannula, is advanced over the wire. The 2 sets in common use are the Accustick introduction system (Meditech/Boston Scientific; Watertown, Mass) and the Neff percutaneous access set (Cook, Inc; Bloomington, Ind).[215]
- After the tip is in the bile duct, the 2 outer fluoropolymer sheaths are advanced over the wire. Once in position, the inner sheath and stiffener are removed, leaving the outer sheath behind. This outer sheath has a 4F inner diameter and a 4F catheter through which a 0.035- or 0.038-inch wire can be passed.[216]
- Cholangiography with further injection of contrast agent can be performed at this stage to improve delineation of the level of obstruction. A 4F catheter with a distal curve (eg, Bernstein catheter) and a 0.035-inch hydrophilic guide wire are usually used to cross the obstructing lesion.
- When the obstruction is high grade and the bile ducts are severely dilated, crossing the obstruction may not be possible. In these cases, external drainage can be tried for a few days to decompress the biliary system, and another attempt can be made later.[217]
- After the catheter is advanced to the duodenum, the wire is exchanged for a stiff guide wire (e.g., Amplatz super stiff wire; Cook, Inc). The catheter and sheath are removed, and a biliary drainage catheter is advanced. A stiff wire is advanced to the small bowel and used to advance the biliary catheter to the small bowel. Various biliary drainage catheters are available. Commonly used catheters have a retaining pigtail loop. The end of this catheter is reformed after the catheter tip is in position in the duodenum and after the inner stiffener is removed.[218-219]
- The proximal side-hole location is checked by injecting contrast material to ensure that it is in the bile duct and not intra parenchymal, as malpositioning may lead to pericatheter leakage or hemobilia. The internal fixation is achieved by using a loop-retaining suture.[220]
- Catheters are also secured to skin by using suture material such as 2-0 polypropylene mesh (Prolene; Ethicon; Piscataway, NJ). The catheter should initially be left to external gravity drainage. A cap can be placed after a few days when the bile is clear of blood and when the patient is afebrile.
- .Patients should be instructed regarding routine catheter care if they are being discharged home after the procedure. The catheter should be flushed with 5-10 mL of sterile water or normal sodium chloride solution at least every 24 hours to prevent debris collection and catheter blockage.[221]
- Catheters should be exchanged every 3-4 months because they are prone to breakage and occlusion over time. Patients should be instructed to uncap the catheter to set it for external drainage in case of the onset of fever. If fever occurs, further investigation is usually necessary because it is presumed to be due to catheter blockage and resultant cholangitis until proven otherwise.[222]

IV. Complication rates

1. Percutaneous trans-hepatic cholangiography

When 21-gauge or smaller needles are used, the major and minor complications of percutaneous trans-hepatic cholangiography should be low. All patients should be treated with appropriate antibiotics before needle puncture.[223]

2. Percutaneous trans-hepatic biliary drainage

- The complication rate for trans-hepatic biliary drainage can be substantial, and varies with preprocedure patient status and diagnosis. Patients with coagulopathies, cholangitis, stones, malignant obstruction, or proximal obstruction will have higher complication rates.[224]
- Several authors have suggested that complications related to internal/external tubes as a result of inadequate bile flow and tube dislodgment (sepsis and hemorrhage) can be minimized by placing a self-retaining tube of at least 10 F through the ampulla or anastomosis.[225]
- All patients should be treated with appropriate antibiotics before initiating the procedures to minimize septic complications. The duration of antibiotic therapy after the procedures will be determined by the clinical course of individual patients.[226]
- Percutaneous trans-hepatic biliary drainage: major complications[227]
- Sepsis
- Hemorrhage.
- Inflammatory/infectious (abscess, peritonitis, cholecystitis, pancreatitis).
- Pleural injury.
- Death.

V. Contraindications

1. Coagulopathy is a relative contraindication to percutaneous trans-hepatic cholangiography, biliary drainage, and every effort should be made to correct or improve coagulopathy before the procedure. In patients with persistent coagulopathy, these procedures may still be indicated if they are associated with a lower expected morbidity rate than alternative methods of diagnosis or treatment.[228]
2. Marked ascites displacing the liver from the abdominal wall and increasing the difficulty of catheter insertion.
3. Other relative contraindications include obese and uncooperative.