

HILAR CHOLANGIOCARCINOMA

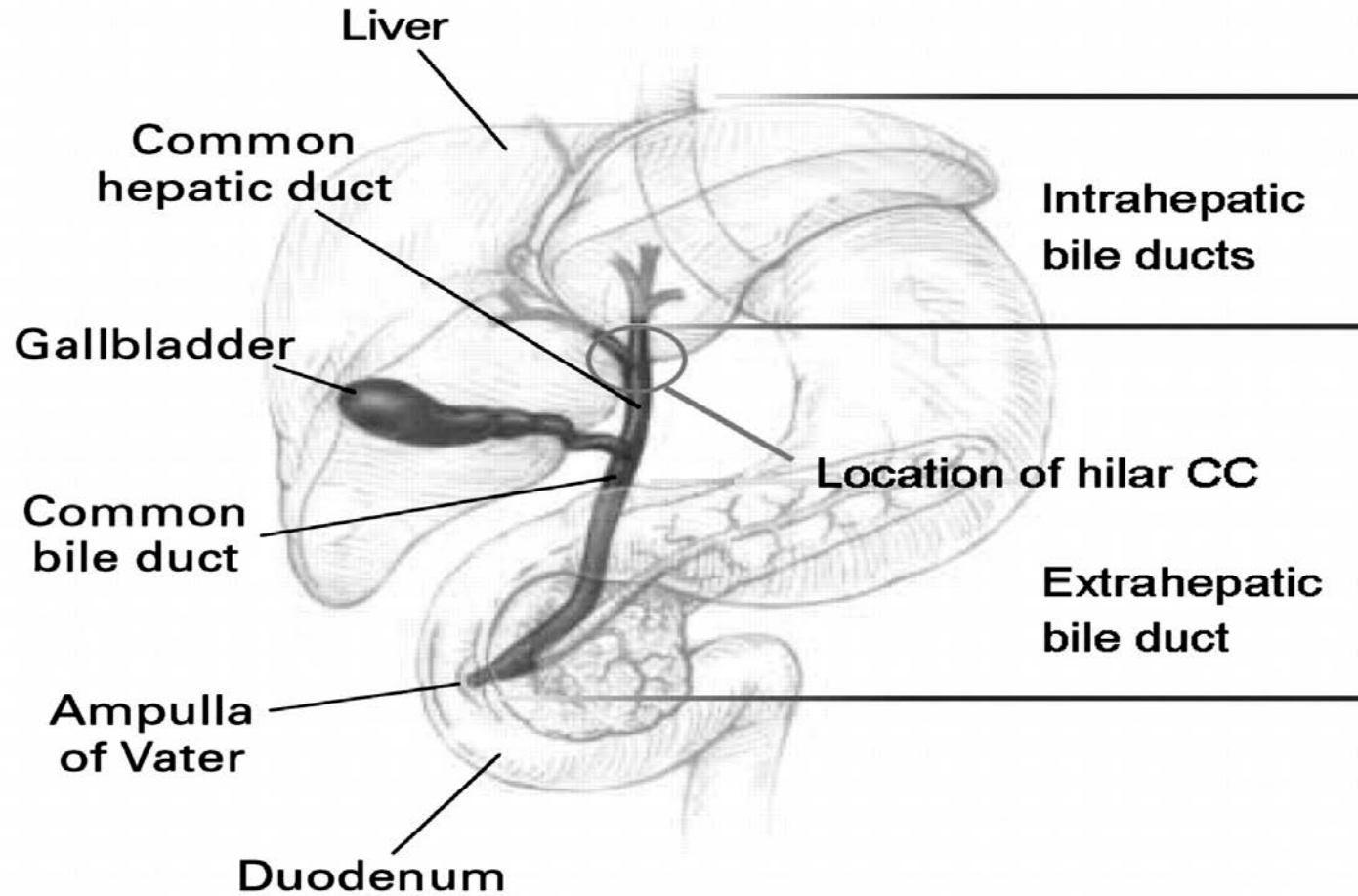
Etiology
Clinical Feature
Management

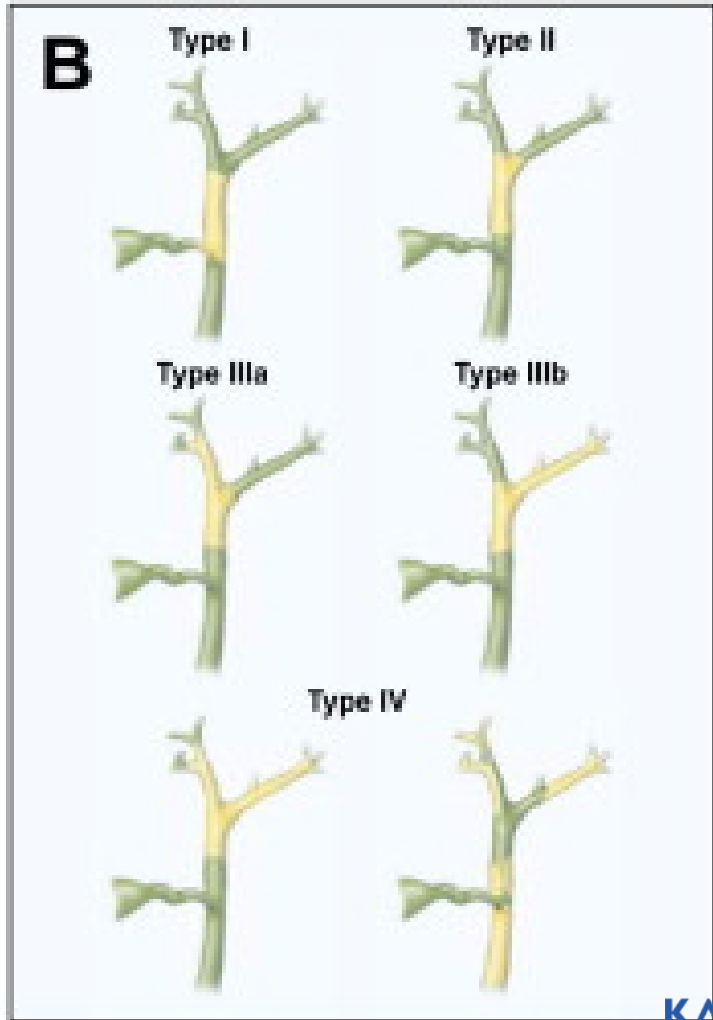
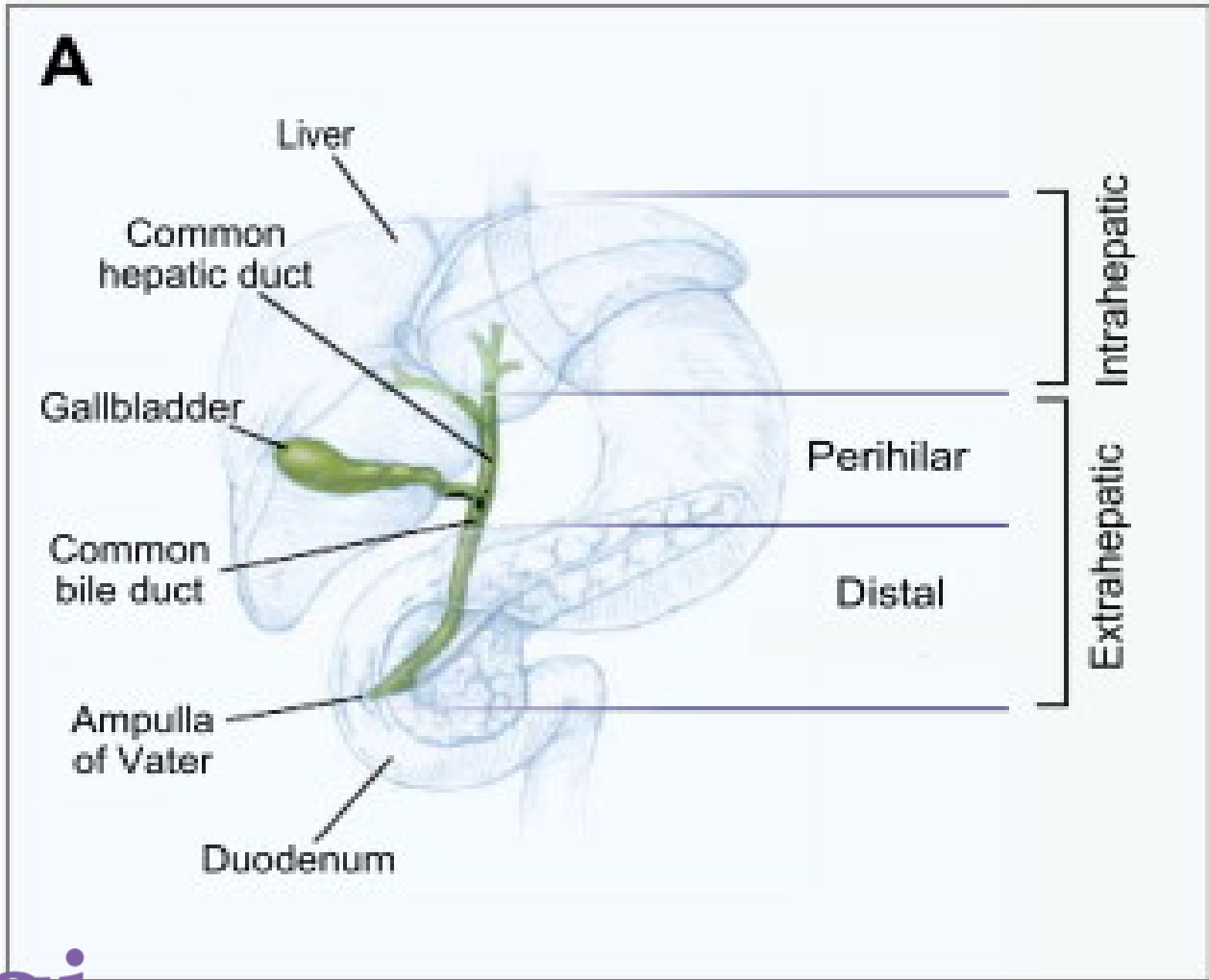
Dr. Alankar Gupta

Incidence

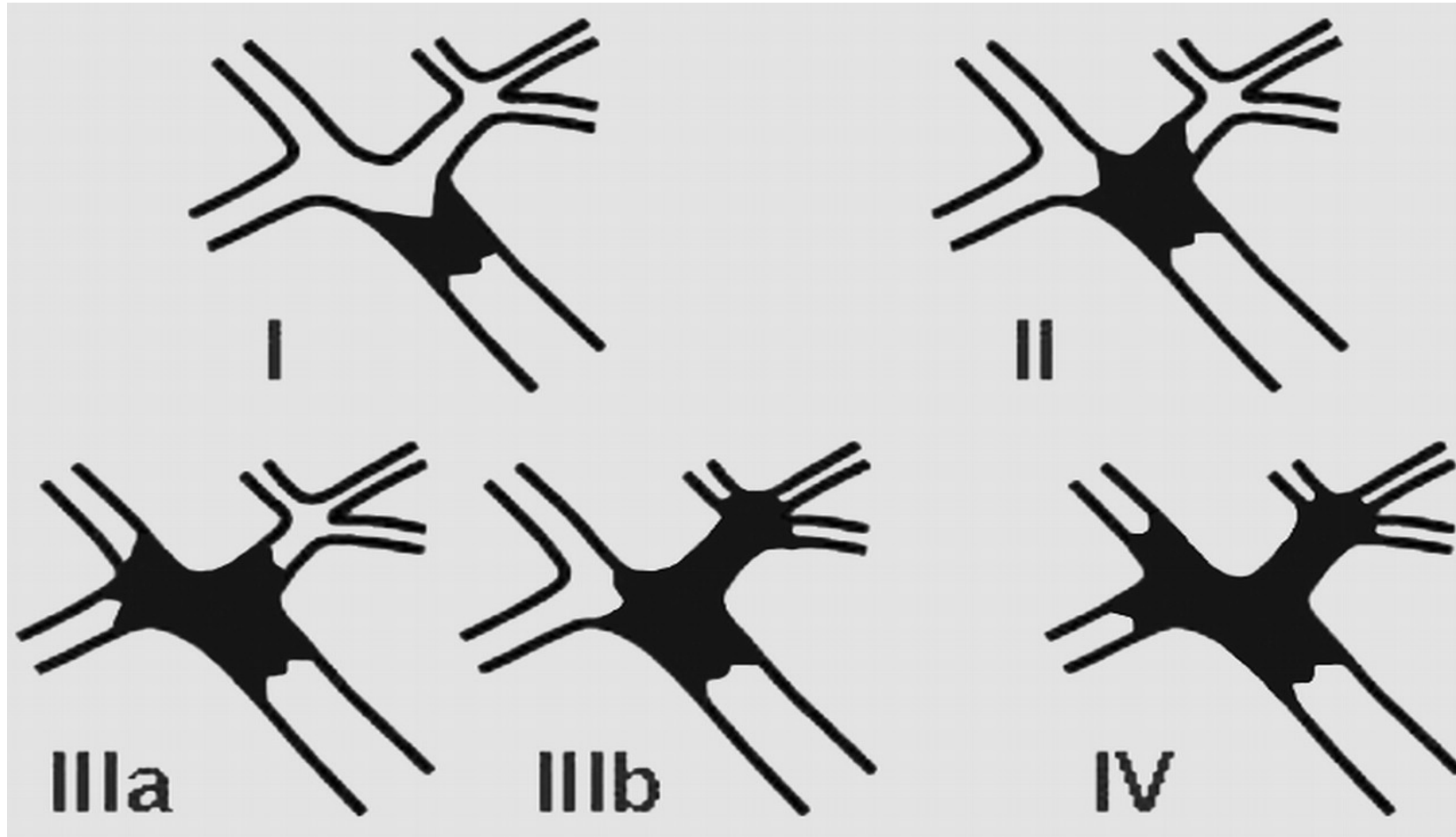
- 3% of all gastrointestinal cancers
- often diagnosed as advanced disease at initial presentation
- a trend has been seen toward older patient age (median range, 65 to 70 years) at the time of diagnosis
- relative increase in the ratio of intrahepatic to extrahepatic cholangiocarcinoma

Anatomy





Bismuth-Corlette classification



Bismuth-Corlette classification

- Tumors below the confluence of the left and right hepatic ducts (Type I)
- Tumors reaching the confluence (Type II)
- Tumors occluding the common hepatic duct and either the right or left hepatic duct (Types IIIa and IIIb, respectively)
- Tumors that are multicentric, or that involve the confluence and both the right or left hepatic duct (Type IV)

Perihilar Colangio CA – TNM Staging

TABLE 6: Staging of perihilar bile duct tumors

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery, and portal vein)
N2	Metastasis to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes

Distant metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a–b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1–3	N1	M0
Stage IVA	T4	N0–1	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

From Edge SB, Byrd DR, Compton CC, et al (eds): AJCC Cancer Staging Manual, 7th ed. New York, Springer, 2010.

Ca Gall Bladder TNM staging

TABLE 5: TNM staging of gallbladder cancer

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or muscular layer
T1a	Tumor invades lamina propria
T1b	Tumor invades muscular layer
T2	Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

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N0	No regional lymph node metastasis
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Stage IIIA	T3	N0	M0
Stage IIIB	T1–3	N1	M0
Stage IVA	T4	N0–1	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

From Edge SB, Byrd DR, Compton CC, et al (eds): AJCC Cancer Staging Manual, 7th ed. New York, Springer, 2010.

Risk Factor

- Primary Sclerosing Colangitis (PSC)
- Fibropolycystic Liver Disease
- Parasitic Infection - Clonorchis and Opisthorchis
- Cholelithiasis
- Hepatolithiasis (recurrent pyogenic colangitis)
- Toxin Exposure
- Lynch Syndrome & Biliary Papillomatosis
- Chronic Liver Disease – HBV, HCV
- Non-viral Chronic Liver Disease
- Diabetes
- Obesity / Metabolic syndrome
- HIV Infection

PSC

- 30 % of cholangio CA are diagnosed in patients with PSC with or without UC
- lifetime risk of Colangio CA is 10 to 15 %
- develops at a significantly younger age (30-50yrs)
- Over one-third of these cases are diagnosed within two years of the initial diagnosis of PSC
- Risk appears unrelated to the duration of the inflammatory disease
- Rapid clinical deterioration with jaundice, weight loss, and abdominal discomfort
- Serum levels of CEA, CA 19-9, CA-50 and CA-242 – not specific

Fibropolycystic Liver Disease

- Caroli's syndrome, congenital hepatic fibrosis, choledochal cysts
- Overall incidence of cholangio CA in patients with untreated cysts is 28 %
- biliary stasis, chronic inflammation from reflux of pancreatic juice

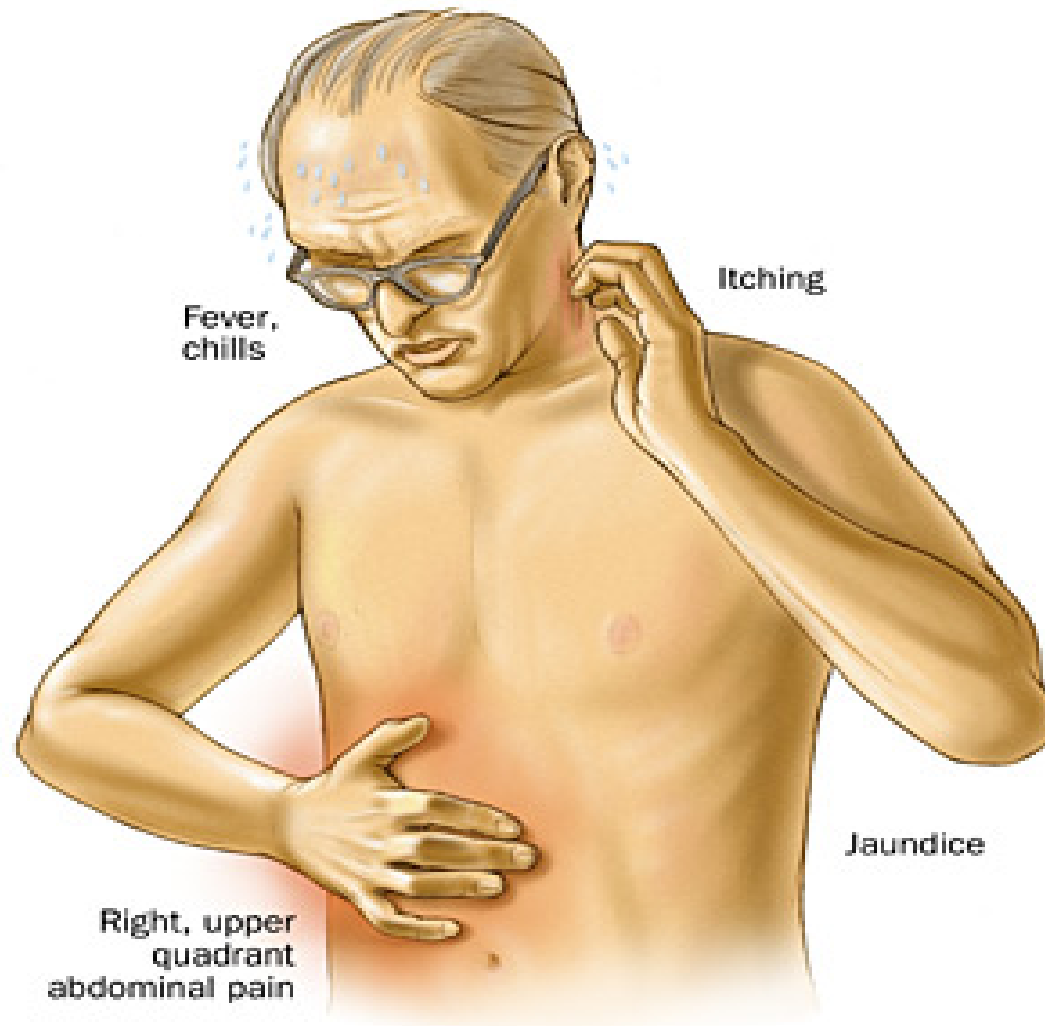
Pathology

- **Adenocarcinoma (90 %)** subdivided into
 - **Sclerosing (scirrhous)** tumors – most common, intense desmoplastic reaction low resectability and cure rates
 - **Nodular** - constricting annular lesion, advanced disease, resectability and cure rates are very low
 - **Papillary** tumors are the rarest – Bulky mass in CBD, highest resectability
- **SCC** – rest of tumor
- IHC Marker - **cytokeratin-7 (CK-7)** positivity is consistent with biliary tract origin

Tumor Characteristics

- Slow growth
- a high rate of local invasion
- Mucin production
- tendency to invade perineural sheaths and spread along nerves
- Lymphnode metastasis is common
- distant **metastases** are distinctly *uncommon*

Symptoms



Fever,
chills

Itching

Jaundice

Right, upper
quadrant
abdominal pain

Clinical Features

- Pruritus (66 %)
- Abdominal pain (30 to 50 %) - constant dull ache in the right upper quadrant
- weight loss (30 to 50 %)
- fever (up to 20 %)
- clay-colored stools and dark urine

Physical Signs

- Jaundice (90 %)
- Hepatomegaly (25 to 40 %)
- Right upper quadrant mass (10 %)

Investigation

- **LFT**
- S.Bilirubin - usually > 10 mg%
- ALT & AST - initially normal, raised in chronic obstruction causing liver dysfunction
- Alk. Phos. - raised > 2 to 10 times
- GGT/5-nucleotidase – raised
- PT/INR - raised in chr. Obstruction causing liver dysfunction

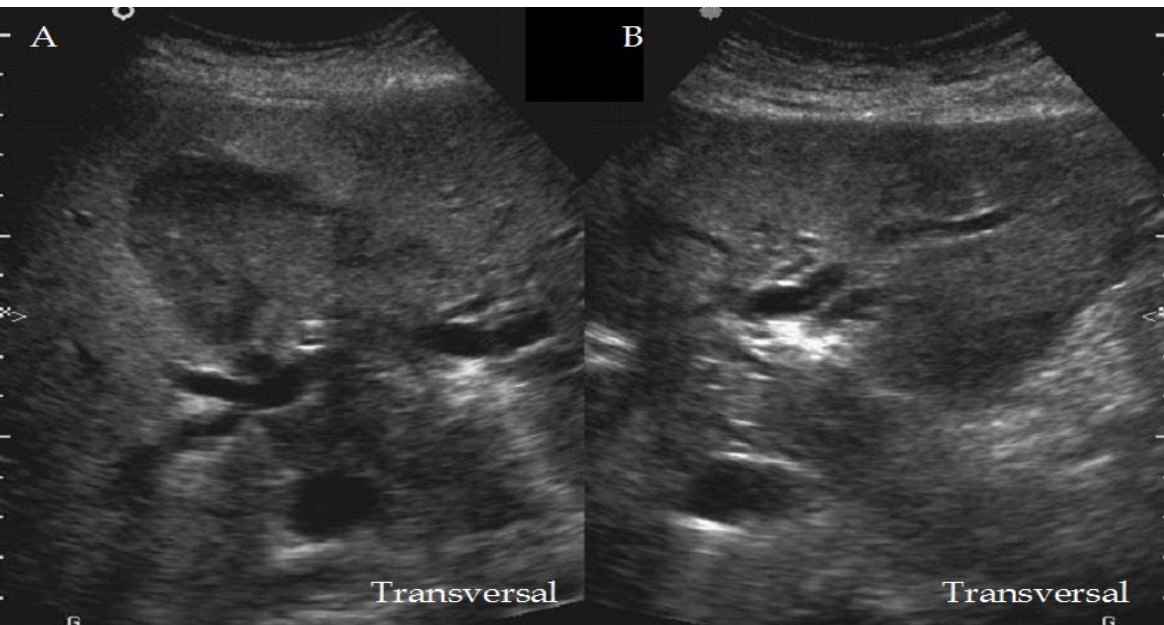
Imaging

- USG Abdomen
- CECT Abdomen
- MRCP
- USG/CT guided biopsy
- ERCP with brushing/biopsy
- CA 19-9

Differential Diagnosis

- Pre-op tissue diagnosis difficult
- 1/3rd patient have benign fibrosis or metastasis from other site.
- Surgical exploration to confirm the diagnosis
- DD
 - Choledocholithiasis
 - benign bile duct strictures (usually postoperative)
 - sclerosing cholangitis
 - compression of the CBD by either chronic pancreatitis or pancreatic cancer

USG Abdomen



- Perihilar and extrahepatic cancers may not be detected
- Indirect signs (ductal dilatation throughout the obstructed liver segments) may point toward the diagnosis
- Klatskin tumors often appear as segmental dilatation and nonunion of the right and left ducts

USG

- Papillary tumors appear as polypoid intraluminal masses
- Nodular cholangiocarcinomas appear as discrete smooth masses with associated mural thickening.

MDCT

- 1) Distant metastasis, including dissemination, liver metastasis, and nodal metastasis
 - 2) Tumor lateral extension or Bismuth classification
 - 3) Vascular invasion with or without lobar atrophy
 - 4) Anatomic variation of the vascular system; and
 - 5) the liver volume of each sector.
-
- Acquisition of three distinct circulatory phases,
 - arterial
 - pancreatic
 - portal venous phases in the pancreatobiliary region with 1-mm collimation
 - Pivotal element of the **preoperative staging** of , and it provides definitive information about **resectability** and **design of resectional procedure**.

MRCP

- replaced endoscopic and percutaneous cholangiography as the initial preoperative assessment
- identify the tumor and the level of biliary obstruction
- may reveal obstructed and isolated ducts
- patency of hilar vascular structures
- presence of nodal or distant metastases
- presence of lobar atrophy

Portal Vein Embolisation

Indication for PVE

- 1) a percentage of FLR of 25% or less in normal liver
- 2) scheduled concomitant extrahepatic surgery or complex hepatectomy
- 3) any major hepatectomy in patients with underlying chronic diseases or with an injured liver (chemotherapy, major steatosis, or cholestasis).

- Abulkhair et al, 2008. Abulkhair A, et al: [Preoperative portal vein embolization for major liver resection: a meta-analysis.](#) *Ann Surg* 2008; 247(1):49-57.
- meta-analysis involving 37 highly selected reports from the literature also supports the utility of PVE
- The choice of device, technique, or embolic agent is generally based on the operator's preference

Techniques for PVE

- *transileocolic portal vein embolization* (TIPE) ([Makuuchi et al, 1990](#))
- *percutaneous transhepatic portal vein embolization* (PTPE) ([Kinoshita et al, 1986](#))
- PTPE is superior to TIPE
- surgeons prefer TIPE to PTPE – diagnostic laprotomy with staging also done.
- The PTPE is done 2 to 4 weeks before surgery, when the total serum bilirubin levels is lower than 5 mg/dL

Pre-op Evaluation

- Four crucial determinants of resectability:
 - 1) extent of tumor within the biliary tree
 - 2) vascular involvement
 - 3) hepatic lobar atrophy
 - 4) metastatic disease
- The presence of significant comorbid conditions, chronic liver disease, or portal hypertension generally precludes resection

Pre – Op biliary drainage

- endoscopic biliary drainage
- percutaneous transhepatic biliary drainage
- The purposes of biliary drainage are summarized as follows:
 - 1) treatment of biliary sepsis
 - 2) relieving jaundice and recovery of functional capacity
 - 3) diagnosis of lateral tumor extension
 - 4) liver function assessment using bile samples
 - 5) improvement of poor food intake

- endoscopic approach versus a percutaneous approach
- unilateral versus bilateral drainage
- All ducts in the FLR should be drained
- endoscopic nasobiliary drainage (ENBD) has been recommended as a preoperative drainage procedure
- PTBD is performed as a second-line procedure only when
 - 1) multiple, separated ducts are present in the FLR
 - 2) total liver drainage is necessary for prolonged cholestasis or segmental cholangitis of the undrained lobe
 - 3) the ENBD tube is dislodged or kinked.

Preoperative Tumor Staging System for Hilar Cholangiocarcinoma

Stage Criteria

- T1 Tumor involving biliary confluence ± unilateral extension to two biliary radicles
- T2 Tumor involving biliary confluence ± unilateral extension to two biliary radicles and *ipsilateral* portal vein involvement ± ipsilateral hepatic lobar atrophy
- T3 Tumor involving biliary confluence + bilateral extension to two biliary radicles or unilateral extension to two biliary radicles with contralateral portal vein involvement or unilateral extension to two biliary radicles with contralateral hepatic lobar atrophy or main or bilateral portal venous involvement

Criteria of Nonresectability in Patients with Hilar Cholangiocarcinoma

- **Patient Factors**
- Medically unfit for operation
- Cirrhosis/portal hypertension
- **Local Factors**
- Hepatic duct involvement up to secondary radicles bilaterally
- Encasement or occlusion of the main portal vein proximal to its bifurcation
- Atrophy of one lobe with encasement of contralateral portal vein branch
- Atrophy of one lobe with contralateral involvement of secondary biliary radicles
- **Distant Disease**
- Histologically proven metastases to lymph node groups beyond the hepatoduodenal ligament (celiac, paraaortic, retropancreatic)
- Histologically proven metastases to liver, lung, or peritoneum

Operative Resection

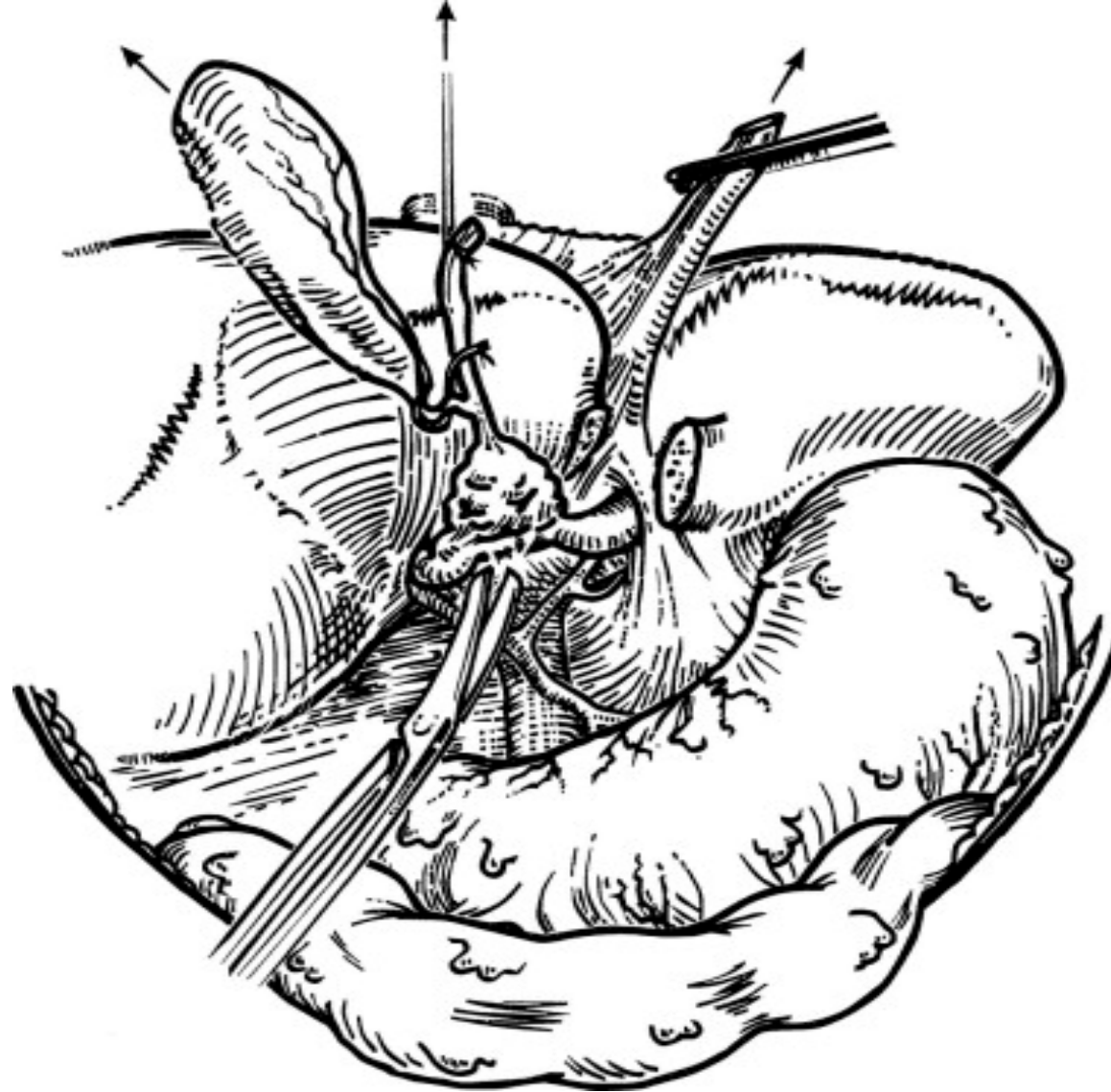
- complete tumor excision with negative margins if possible
- restoration of biliary-enteric continuity from an adequate liver remnant
- Orthotopic liver transplantation - 5-year survival of 17%
- complete removal of all gross disease with clear histologic margins (R0 resection)
- Achieving an R0 resection almost always requires a partial hepatectomy

Local resection

- Resection of the extrahepatic biliary apparatus without concomitant partial hepatectomy—for small Bismuth-Corlette type I tumors not involving the major vessels.
- local resections seem to be inferior with respect to long-term survival
- Achieving an R0 resection almost always requires a partial hepatectomy
- en bloc caudate lobectomy is frequently necessary

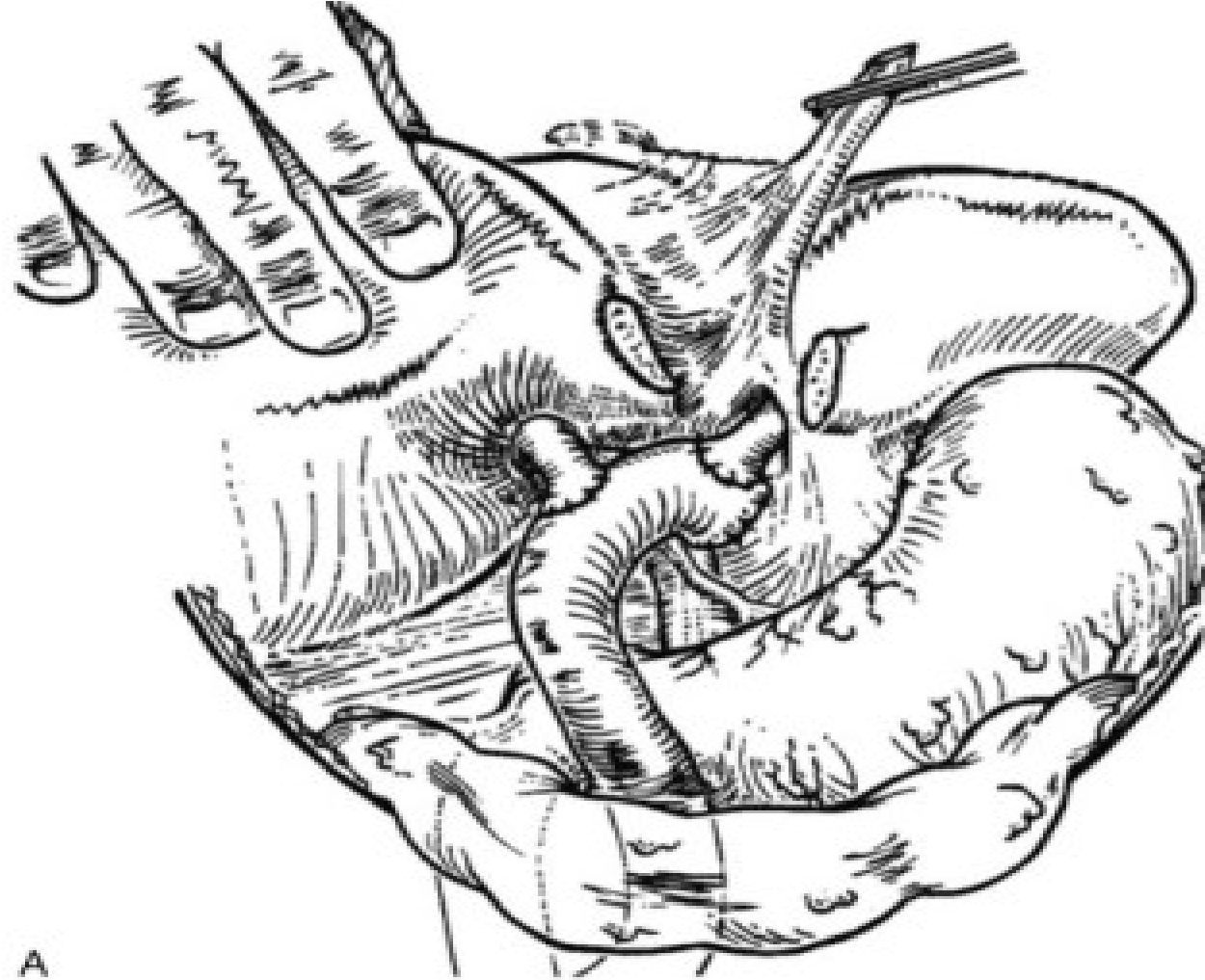
Operative Exploration

- “hockey stick” incision
- inspection of the peritoneal cavity and distant nodal sites
- bimanual palpation of the liver and intraoperative US
- Palpation of the caudate lobe is performed after incision of the lesser omentum
- Kocher maneuver - retroduodenal lymph nodes
- ligamentum teres is elevated, exposing the undersurface of the liver - examination of the subhilar and retroduodenal area



The entire extrahepatic biliary apparatus is elevated together with associated portal connective tissue and nodes to allow dissection anterior to the bifurcation of the portal vein and elevation of the tumor, which is now completely mobilized.

The hepatic artery and portal vein are skeletonized.



In rare circumstances, the extrahepatic biliary tree can be excised alone with curative intent without the need for partial hepatectomy. In other situations, tumor unresectability may not be determined until the extrahepatic bile ducts are divided. The exposed right and left hepatic ducts are anastomosed individually to a retrocolic Roux-en-Y loop of jejunum. **B**, Retrograde transhepatic biliary stents can be passed at the time of operation to provide long-term palliation of obstructive jaundice and facilitate photodynamic therapy.

- Optimal procedure (extensive vs. limited surgery) for Bismuth type I and II tumors is still under debate
- right-sided hepatectomy is suitable for nodular or flat tumors that display an infiltrating nature in the advancing margin
- limited surgery—including resection of S1, S1+4, or bile duct resection alone—is acceptable for papillary tumors, provided the surgical margin is negative

- *superficial spreading type cholangiocarcinoma*
- noninvasive cancer extension longer than 2 cm
- complete eradication of the superficial spreading lesion (in situ carcinoma) is necessary
- extensive surgery, such as hepatopancreatoduodenectomy
- Multiple tumors – 5 to 9 %

Hepatectomy

- left hemihepatectomy
- right hemihepatectomy
- right trisegmentectomy
- left trisegmentectomy
- liver transplantation and partial pancreatoduodenectomy (LTTP)

Lymph Node Dissection

- Some authors have reported long-term survivors, even with involved paraaortic lymph nodes, and have argued for extended lymphadenectomy as a routine part of the resection procedure ([Kitagawa et al, 2001](#)).
- involved lymph nodes are a powerful adverse prognostic variable
- metastatic involvement of distant lymph node basins (N2 disease) to represent unresectable disease

Adequate lymph node assessment for extrahepatic bile duct adenocarcinoma.

Ito K, Ito H, Allen PJ, Gonen M, Klimstra D, D'Angelica MI, Fong Y, DeMatteo RP, Brennan MF, Blumgart LH, Jarnagin WR

Ann Surg. 2010 Apr; 251(4):675-81.

- Ito *et al.* demonstrated the relationship between the total number of LN examined and survival in patients without LN metastasis
- Ito *et al.* identified an optimum cut-off value for hilar cholangiocarcinoma of **seven LN** for a higher disease-specific survival for N0 patients

Prognostic significance of lymph node ratio after resection of peri-hilar cholangiocarcinoma

- HPB (Oxford). 2011 April; 13(4): 240–245.
- According to 7th edn the *AJCC/UICC Guidelines* at least **three** LN should be harvested for adequate staging of perihilar cholangiocarcinoma.
- Lymphadenectomy of the regional lymph nodes was classified according to the classification of the Japanese Society of Biliary Surgery.
- Lymph nodes of the hepatoduodenal ligament (12h, 12a, 12p, 12b), the proper hepatic artery (8) and of the posterior surface of the head of the pancreas (13) were routinely dissected and retrieved; interaortocaval lymph nodes were retrieved when macroscopically abnormal.
- The number of LN harvested and LNR showed a prognostic value.

Systematic review and meta-analysis of the **role of vascular resection** in the treatment of hilar cholangiocarcinoma.

[Abbas S](#), [Sandroussi C](#).

Source

Department of Hepatobiliary Surgery, Royal Prince Alfred Hospital, Sydney, NSW, Australia.

- [HPB \(Oxford\)](#). 2013 Jul;15(7):492-503
- Portal vein resection does not preclude curative resection; however, it is not routinely recommended unless there is suspicion of tumour invasion. There was no proven survival advantage with portal vein resection.
- Arterial resection results in higher morbidity and mortality with no proven benefit.

Outcomes after Operation

- Long-term survival can be achieved with an acceptable operative mortality
- Five-year survival rates range from 25% to 40%
- Operative mortality < 10 %
- Major cause of mortality – Liver Failure after major resection
- Mortality reduced by pre-op biliary drainage and PVE
- Use of hepatic resection - increases in the percentage of R0 resections (negative histologic margins)
- Other determinants :
 - tumor involvement of regional lymph nodes
 - tumor grade or differentiation
 - tumor morphology

- It has long been assumed that survival after resection of distal bile duct tumors is greater than after resection of hilar cholangiocarcinomas
- If adjusted for stage and completeness of resection, the survival rates seem to be comparable ([Allen et al, 2008](#); [Nagorney et al, 1993](#)).

Adjuvant Therapy after Operative Resection

- At present, no data are available to support the routine use of adjuvant or neoadjuvant radiation therapy
- no benefit of adjuvant systemic 5-fluorouracil (5-FU) and mitomycin C compared with surgery alone - [Takada and associates \(2002\)](#)
- Adjuvant therapy (chemotherapy and/or radiation therapy) after resection has not been shown to improve survival

Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma.

[Rea DJ](#), [Heimbach JK](#), [Rosen CB](#), [Haddock MG](#), [Alberts SR](#), [Kremers WK](#), [Gores GJ](#), [Nagorney DM](#).

Source

Division of Gastroenterologic & General Surgery, Mayo Clinic College of Medicine, Rochester, MN, USA.

- [Ann Surg.](#) 2005 Sep;242(3):451-8; discussion 458-61
- Liver transplantation with neoadjuvant chemoradiation achieved better survival with less recurrence than conventional resection
- 5 year survival approx 80 %

Palliative Therapy

- Most patients with hilar cholangiocarcinoma are not suitable for resection
- Indication for **biliary decompression**
 - relieve intractable pruritus
 - treat cholangitis
 - gain access for intraluminal radiotherapy
 - allow recovery of hepatic parenchymal function in patients who are potential candidates for chemotherapy
- Jaundice alone, without pruritus or cholangitis, is **not** an indication for biliary decompression
- **Supportive care** alone is probably the best approach for elderly patients with significant comorbid conditions

- Patients who are found to be unresectable at operation - operative biliary decompression - hepaticojejunostomy or intrahepatic biliary-enteric bypass,
- segment III bypass - 1-year bypass patency 80%
- If the patient is deemed unresectable, the diagnosis should be confirmed with a biopsy

Biliary Decompression

- Percutaneous transhepatic puncture
- endoscopic stent placement – difficult
- The failure rates and incidence of subsequent cholangitis after endoscopic drainage can be high
- Satisfactory drainage of only 25% to 30% of functional hepatic parenchyma is required for resolution of jaundice
- two or more uncovered stents must be placed for adequate drainage
- Bilateral drainage is not better or more effective than unilateral drainage
- Percutaneous drainage through an atrophic lobe does not relieve jaundice and should be avoided

- The median patency of metallic endoprostheses at the hilus is approximately 6 months
- stent occlusion requiring reintervention occurs in 25% of patients

Palliative radiation therapy

- A combination of external beam radiation (5000 to 6000 cGy) and intraluminal iridium-192 (2000 cGy) delivered percutaneously is typically used
- improved survival compared with biliary decompression alone has not been documented
- Episodes of cholangitis and intermittent jaundice were relatively common

Photodynamic therapy

- First, a photosensitizer is injected; second, direct illumination via cholangioscopy activates the compound, causing tumor cell death. [Ortner and colleagues \(1998\)](#)

Internal Drainage and Bile Replacement

- superiority of internal biliary drainage
- bile replacement is essential to maintain intestinal barrier function
- bile replacement during external biliary drainage

Inchinkoto and Ursodeoxycholic Acid

- Ursodeoxycholic acid (UDCA) is a major primary bile acid
- several effects on hepatocytes: protection against oxidative stress, inhibition of apoptosis, stimulation of bile flow, detoxification of cholephilic compounds, and immunomodulation
- widely used for cholestatic liver disease

Synbiotic Administration

- *Lactobacilli* and *Bifidobacteria* are widely used as **probiotics**
- Several types of ingredients, such as fructooligosaccharides, galactooligosaccharides, and inulin, are used as **prebiotics**.
- The combined use of probiotics and prebiotics is called *synbiotics*
- synbiotics can reduce postoperative infections - RCT

Thank You