- **ID:** 55y Male
- **CC:** Recurrent RUQ and Epigastric pain x 1 month.
- **PI:** The patient complains of a 1-month history of abdominal pain. He describes it as having "colic" characteristics, but notes a persistent dull ache between episodes. The pain is not relieved by antacids. The patient gives a history of 6 kg weight loss during 1 month.
- **Physical Exam:**
- **Abd:** Soft, non-tender, no palpable masses. Murphy's sign negative.
- **Vitals:** BP 130/70, HR 87, SpO2 95% ,RR 18

- **Lab data:** WBC:4100, Hg:14.8, Plt:140K, Urea:23, Cr:1.17, Na:140, K:4.4, Bili Total:2.1, direct:1.4, CRP=4, AST:57, ALT:50, ALP:619

سونولوگرافی کامل شکم و لگن:

کبد با اندازه و شکل طبیعی رویت شد.
اکوژنیسیته پارانشیم کبد هتروژن می‌باشد. تطابق با **LFT** توصیه می‌شود.
پهنای صفراوی خارج کبدی و نیز قطر مجرای صفراوی نرمال می‌باشد.
مجاری صفراوی داخل کبدی به صورت دیلاته رویت شد.
CBD در قسمت‌های پروگزیمال **۷.۵ میلی‌متر** رویت شد.

کیسه صفرا فاقد اتساع با ضخامت جداری نرمال رویت شد.
اندازه، اکوژنیسیته پارانشیم و شکل کیسه صفرا طبیعی می‌باشد.
سنگ کیسه صفرا و اسلاج در داخل آن رویت نشد.

سونوگرافی از پانکراس به‌علت گازهای روده‌ای ارزشی نداشت.
اندازه حدود و اکوژنیسیته پارانشیم هر دو کلیه نرمال رویت می‌شود.
ضایعه فضاگیر به دو صورت **Solid** و **Cystic** در کلیه‌ها مشاهده نشد.
هیدرونفروز در کلیه‌ها مشاهده نشد.

طحال به حجم **۳۰ سی‌سی** رویت شد.
مایع آزاد در حفره شکم و لگن مشاهده نشد.

سونولوگرافی از نظر آپاندیس RLQ:

در بررسی ناحیه **RLQ** در حال حاضر یافته‌ای دیده نمی‌شود.
در صورت تداوم علائم یا یافته‌های بالینی و آزمایشگاهی، سونوگرافی کنترلی توصیه می‌شود.

Spiral Abdominopelvic Ct Scan With and without (IV & ORAL) Contrast

Liver: evidence of hetero dense enhancing mass lesion measured about 39*25 mm with involvement of common hepatic bile duct and origin of left and right hepatic ducts and the part of CBD is seen. that is **infavor** of perihilar cholangiocarcinoma for first DDX.

Significant dilation of intrahepatic bile ducts in both lobes is noted.

Mild Distension of gallbladder is seen.

Evidence of calcified stone in gallbladder measured 6 mm is noted.

Evidence of enhancing nodule measured 13 mm in segment VI of liver is seen. (metastatic nodule?) another hypodense nodule measured 4 mm in segment VIII of liver is seen that is not characteristic because of small size.

Evidence of porta hepatis lymph nodes with most diameter 22*13 mm are seen.

Tortuosity and dilation of vasculature structure in porta hepatis are seen.

Significant narrowing of apart of portal vein is seen that is **infavor** of tumor invasion.

Pancreas: normal size and density for age without duct dilation or mass. No peripancreatic fluid collection.

Spleen: normal size and density

Adrenal glands: normal size and density

Spiral CT scan of Chest (with IV Contrast):

Multislice axial images with IV contrast administration reveal:

Lungs: normal pulmonary aeration and interstitial, bronchial and vascular markings. No mass, nodule, infiltration, or bronchial abnormality.

Pleural reflections: No pleural thickening or effusion

Mediastinum: unremarkable

Heart: unremarkable

Chest wall: unremarkable

Adrenal glands: normal size and density

Rt Kidney: normal size, density and parenchymal thickness without hydronephrosis, cyst, stone or mass.

Lt Kidney: normal renal size, density and parenchymal thickness without hydronephrosis, cyst, stone or mass.

no abnormal enhancement.

Aorta, IVC and retroperitoneum: unremarkable. No para-aortic lymphadenopathy.

Ascites: none

Bowel loops, other soft tissues and bony structures: unremarkable

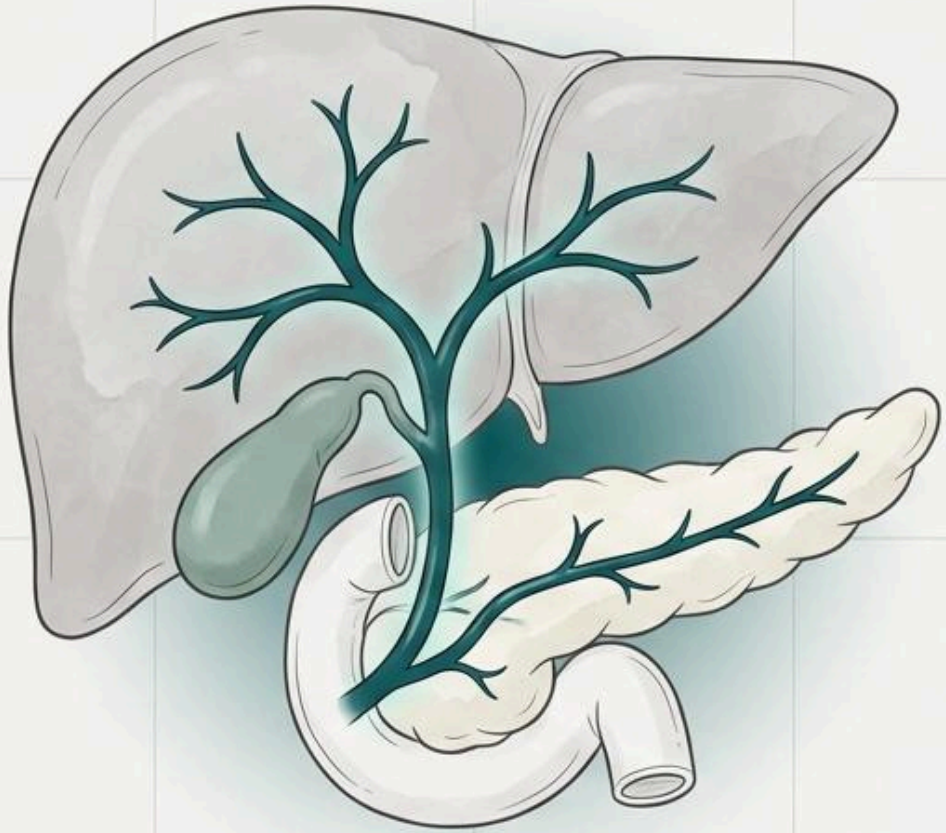
Bladder: normal wall thickness. No mass or stone.

MRCP:

Sever dilatation of intrahepatic bile ducts are noted with associated abrupt narrowing at right and left common hepatic duct confluence, most likely suggestive of mass lesion such as **klatskin tumor**
CBD: 4 mm

So for further evaluation **three phasic liver CT scan is highly suggested.**

The size of gallbladder and its borders are normal with homogenous contents.
The position, caliber and intraluminal signal within the pancreatic duct is normal.

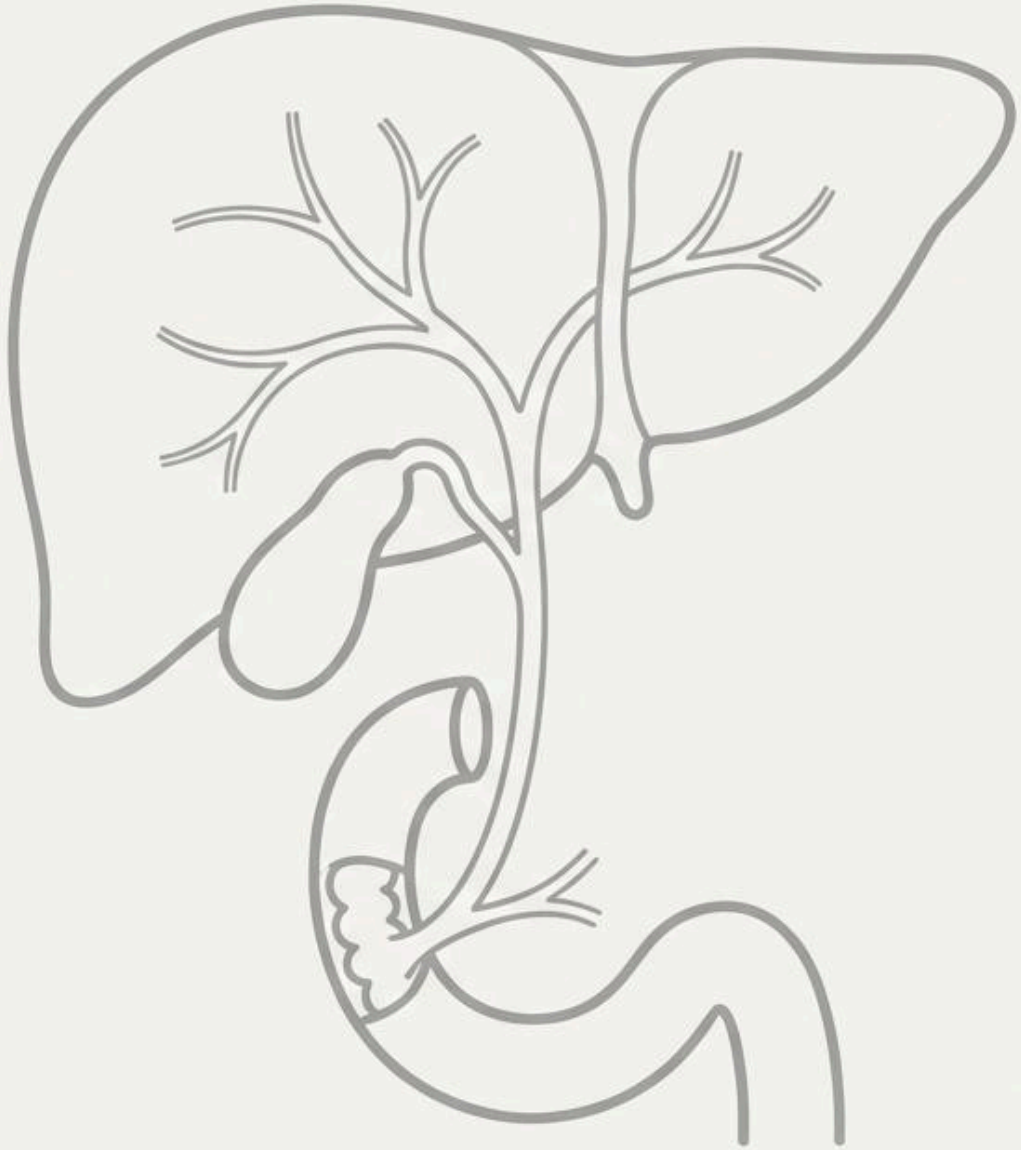


Understanding Cholangiocarcinoma

A Comprehensive Clinical Masterclass on a Rare and Lethal Malignancy

Cholangiocarcinoma is a rare malignancy arising from the bile duct epithelium.

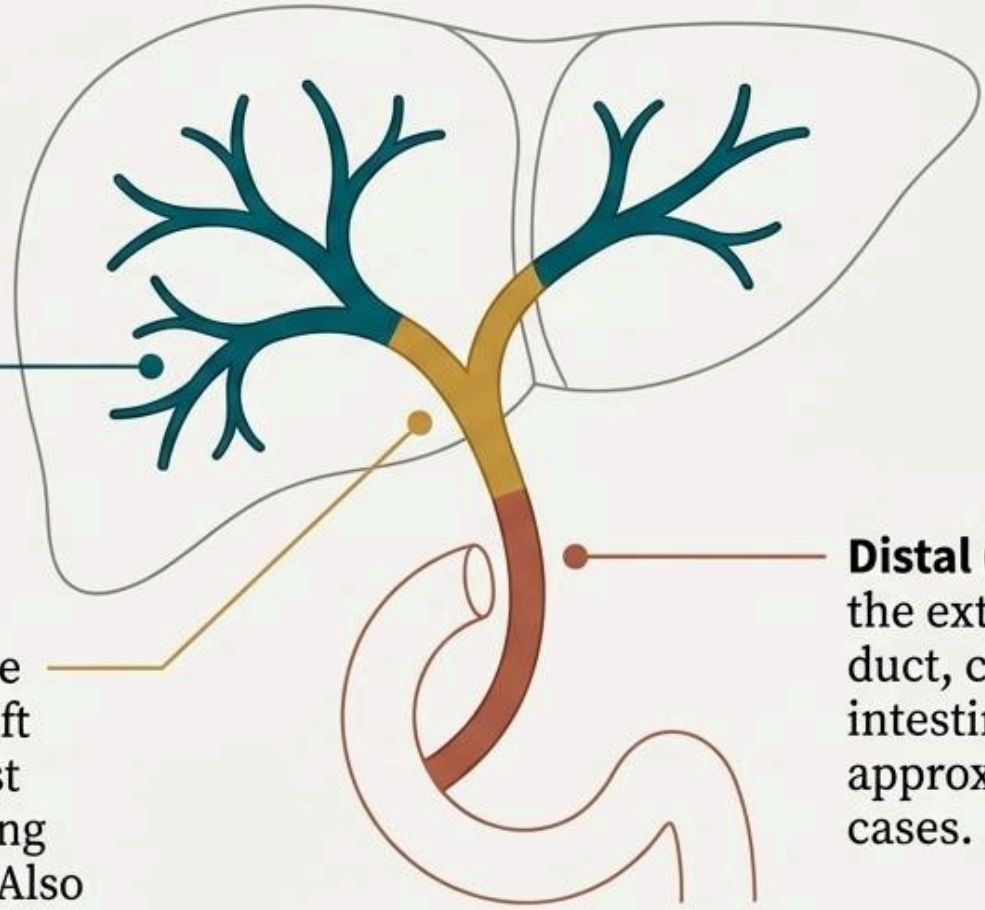
- A group of highly lethal cancers originating from the epithelial cells of the intrahepatic and extrahepatic bile ducts.
- Most cases are locally advanced at presentation, contributing to a poor prognosis.
- It is anatomically and pathologically distinct from gallbladder cancer or ampulla of Vater Vater cancer, even though they are part of the same biliary drainage system.



The cancer is classified by its anatomical location within the biliary tree.

Tumors are categorized into three main groups based on where they originate. This classification dictates the clinical approach and prognosis.

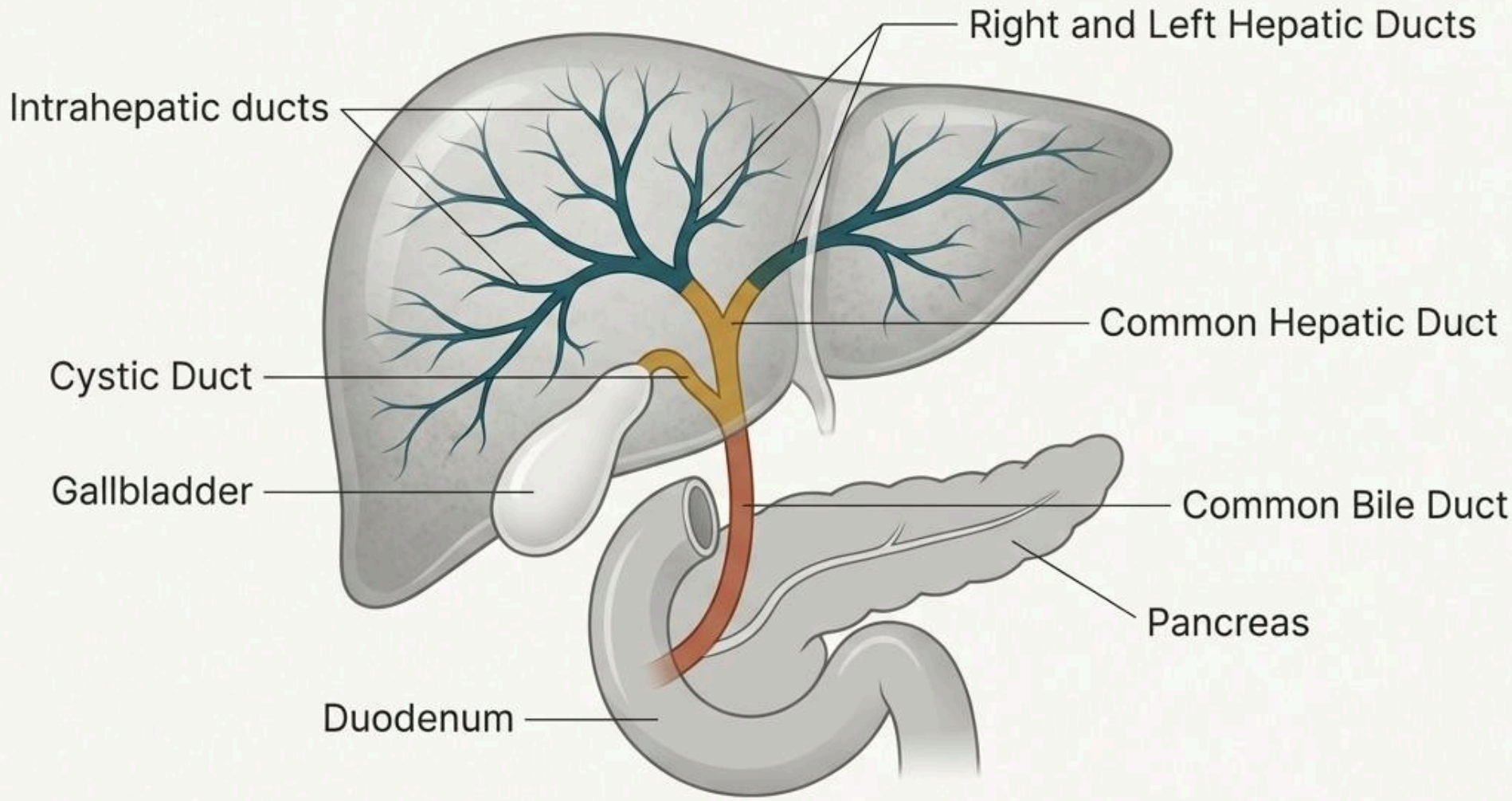
Intrahepatic (iCCA): Arises from bile ducts *within* the liver. Accounts for less than 10% of cases.



Perihilar (pCCA): Arises at the confluence of the right and left hepatic ducts. This is the most common location, representing approximately 50% of cases. Also known as a “Klatskin tumor.”

Distal (dCCA): Arises in the extrahepatic bile duct, closer to the small intestine. Accounts for approximately 40% of cases.

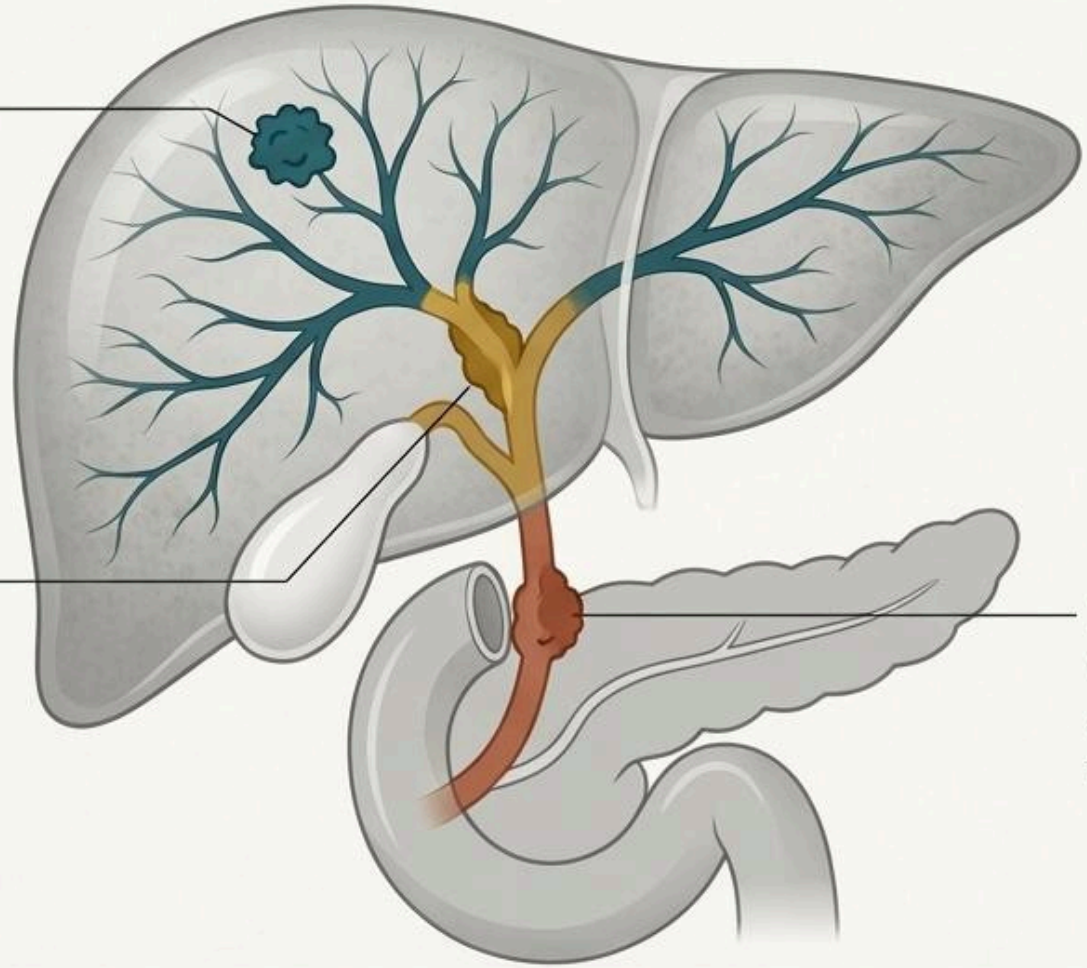
Biliary Anatomy



Tumor location dictates the classification and surgical approach.

Intrahepatic (iCCA): Originates from small intrahepatic ductules (peripheral) or large intrahepatic ducts proximal to the bifurcation.

Perihilar (pCCA / Klatskin Tumor): Involves the common hepatic duct bifurcation, where the left and right hepatic ducts join.

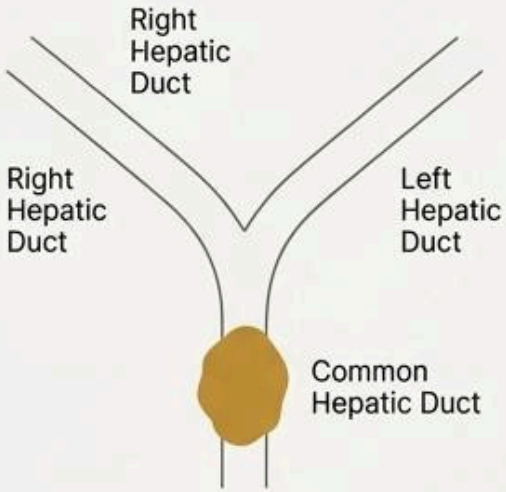


Distal (dCCA): Occurs in the extrahepatic bile duct segment that runs behind the duodenum.

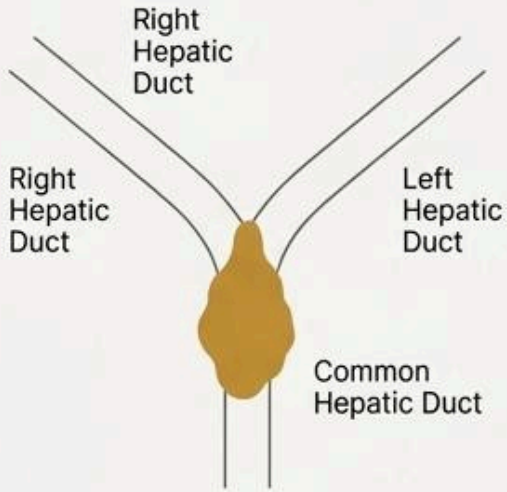
Surgical management is individualized according to the location of the tumor within the biliary tree.

The Bismuth-Corlette system classifies perihilar tumors by the extent of ductal involvement.

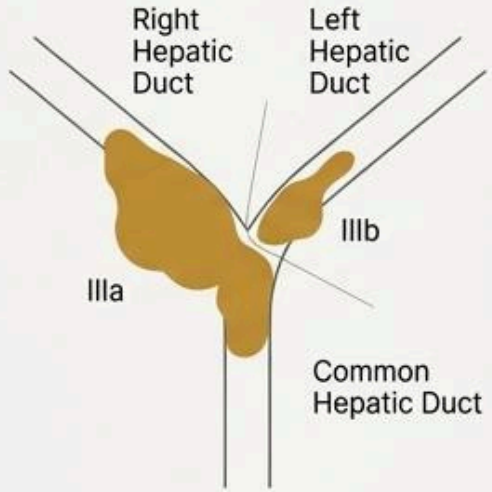
Cancers arising in the perihilar region are further sub-classified according to their patterns of involvement of the hepatic ducts. This system is critical for determining surgical strategy.



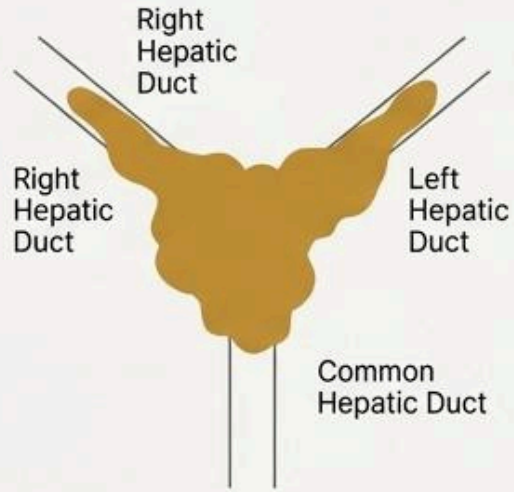
Type I: Tumor is below the confluence of the left and right hepatic ducts.



Type II: Tumor reaches the confluence.

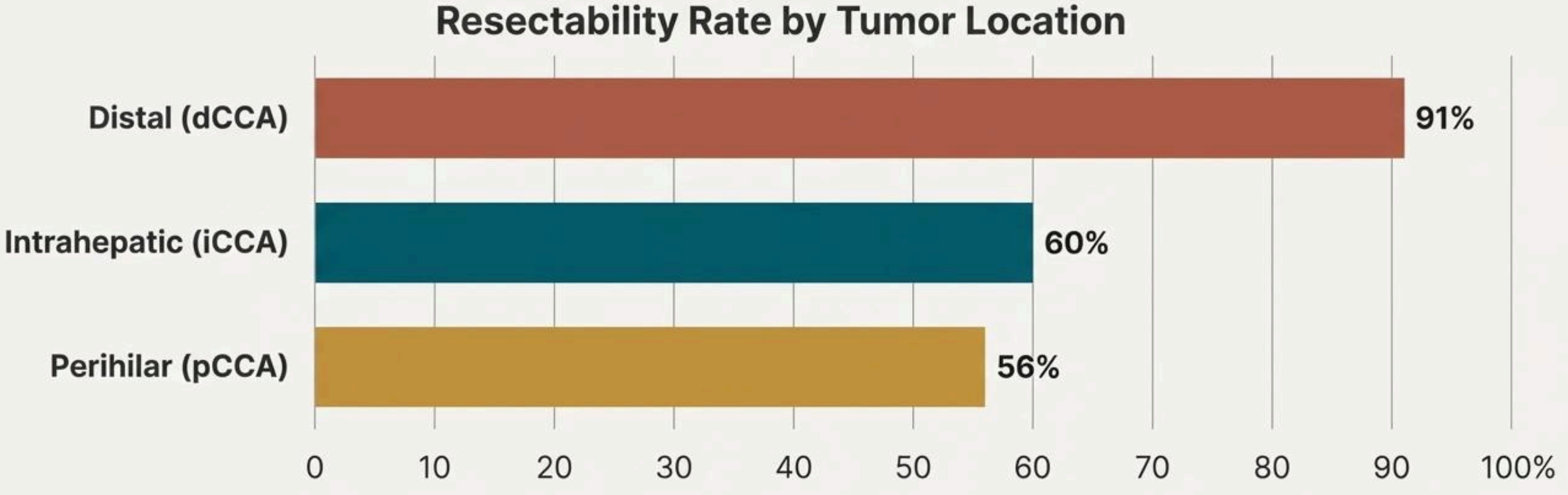


Type IIIa / IIIb: Tumor occludes the common hepatic duct and extends into either the right (IIIa) or left (IIIb) hepatic duct.



Type IV: Tumor involves the confluence and extends into both the right and left hepatic ducts, or is multicentric.

Anatomic location is a key determinant of resectability and prognosis



Clinical Insight: Unfortunately, neither the Bismuth-Corlette classification nor the AJCC's TNM staging accurately assesses resectability, and true resectability may be ultimately determined only at surgical exploration.

Cholangiocarcinoma incidence reveals dramatic global and regional disparities

Cholangiocarcinomas account for approximately 3% of all gastrointestinal malignancies.

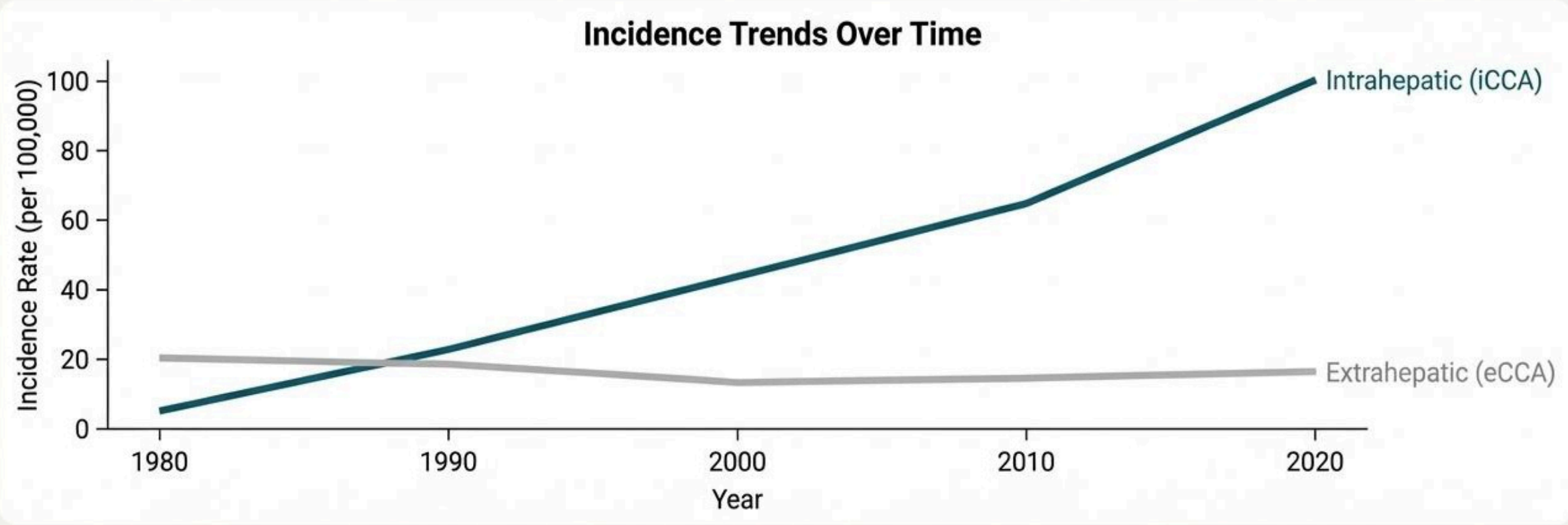
Low-Incidence Regions (e.g., United States, Europe)

- Considered a rare cancer.
- Incidence: 0.35 to 2 cases per 100,000 population per year.
- The US SEER database suggests an incidence of 1.26 cases per 100,000, with two-thirds of cases being intrahepatic.

High-Incidence Endemic Regions (e.g., Thailand, China)

- Incidence is up to 40-fold higher.
- Driven by specific regional risk factors, primarily chronic infection with liver flukes (eg, *Opisthorchis viverrini*).

The incidence of intrahepatic cholangiocarcinoma has been rising for four decades.

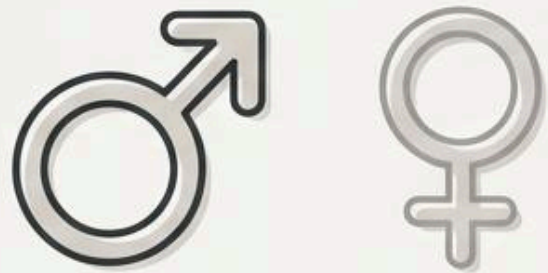


Key Trends

- The incidence and mortality of intrahepatic cholangiocarcinoma (iCCA) have been rising globally over the past 40 years.
- In contrast, rates of extrahepatic cholangiocarcinoma (eCCA) had been declining until approximately the year 2000, but more recent reports suggest a potential increase as well.
- This is considered a true increase, not an artifact of better diagnosis, as it is not associated with a shift toward detecting smaller or earlier-stage lesions.

Demographic factors define the typical patient profile

- **Age:** Incidence increases with age. The typical patient is between **50 and 70 years years old.**
- **Exception:** Patients with pre-existing conditions like Primary Sclerosing Cholangitis (PSC) or choledochal cysts often present nearly **two decades earlier**, typically between the ages of 30 and 50.
- **Gender:** There is a slight male predominance, which likely reflects the higher incidence of PSC in men.



The Patient's Story: Obstructive and Systemic Symptoms

The clinical presentation of cholangiocarcinoma is dominated by the consequences of biliary obstruction, particularly in extrahepatic tumors. However, constitutional symptoms are also common and point toward a potential underlying malignancy.

Signs of Biliary Obstruction (Cholestasis)

Jaundice: Yellowing of the skin and eyes. The most common presenting sign.

Pruritus: Intense, generalized itching.

Dark Urine: Caused by the excretion of conjugated bilirubin.

Pale or Clay-Colored Stools: Resulting from the lack of bilirubin reaching the gut.

Constitutional & Abdominal Symptoms

Abdominal Pain: Often a constant, dull ache in the right upper quadrant.

Weight Loss: Unintentional and significant.

Malaise & Fatigue: A general sense of unwellness.

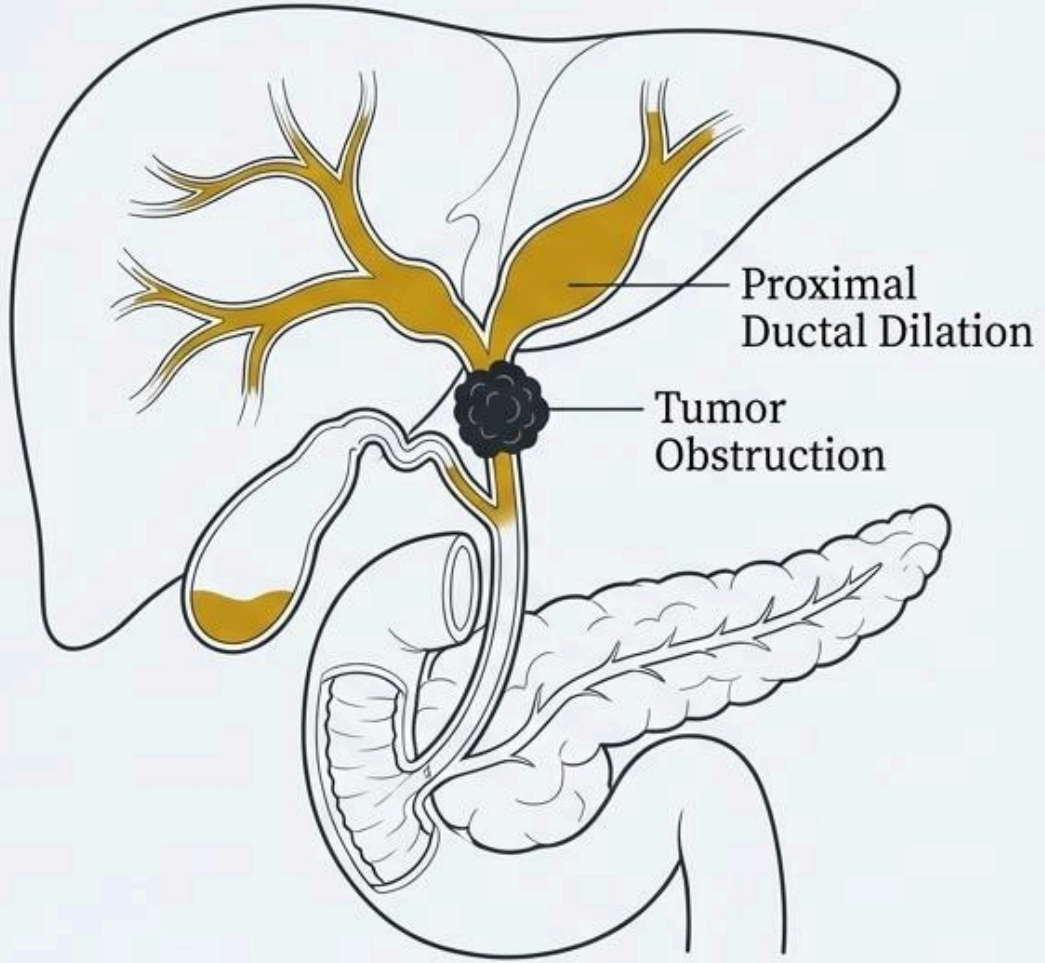
Fever: Can occur in up to 20% of patients.

Jaundice is the Hallmark of Extrahepatic Disease

90%

Jaundice is the presenting symptom in 90% of patients with extrahepatic cholangiocarcinoma. It is caused by the tumor obstructing the biliary drainage system, leading to a buildup of bilirubin in the blood.

- Often described by patients as painless, especially in the early stages.
- Accompanied by other cholestatic signs: pruritus, dark urine, and clay-colored stools.
- The presence of jaundice should always prompt an investigation to exclude malignancy.



Abdominal Discomfort and Systemic Decline are Common

Beyond the classic signs of jaundice, many patients report significant abdominal pain and constitutional symptoms that reflect the systemic impact of the malignancy.

Abdominal Pain

30 to 50%

Character: Typically a constant, dull ache in the right upper quadrant (RUQ).

Weight Loss

30 to 50%

Character: Unexplained and often progressive, signaling a catabolic state.

Weight Loss

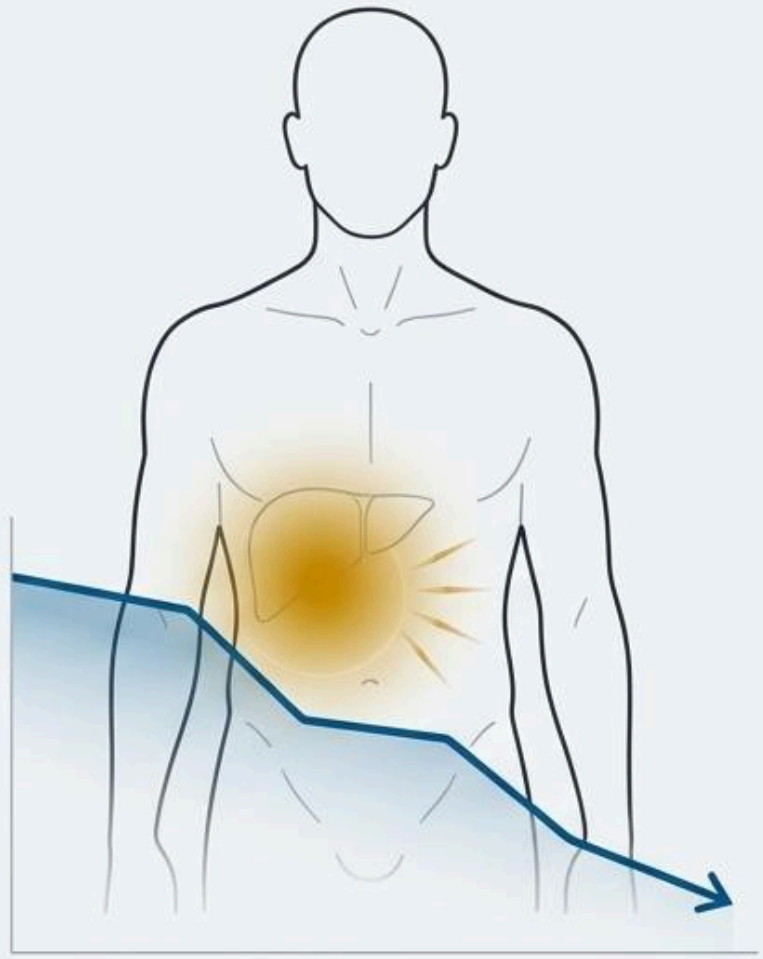
30 to 50%

Character: Unexplained and often progressive, signaling a catabolic state.

Fever

Up to 20%

Note: Cholangitis is an unusual initial presentation but can occur.



From Patient History to Physical Examination

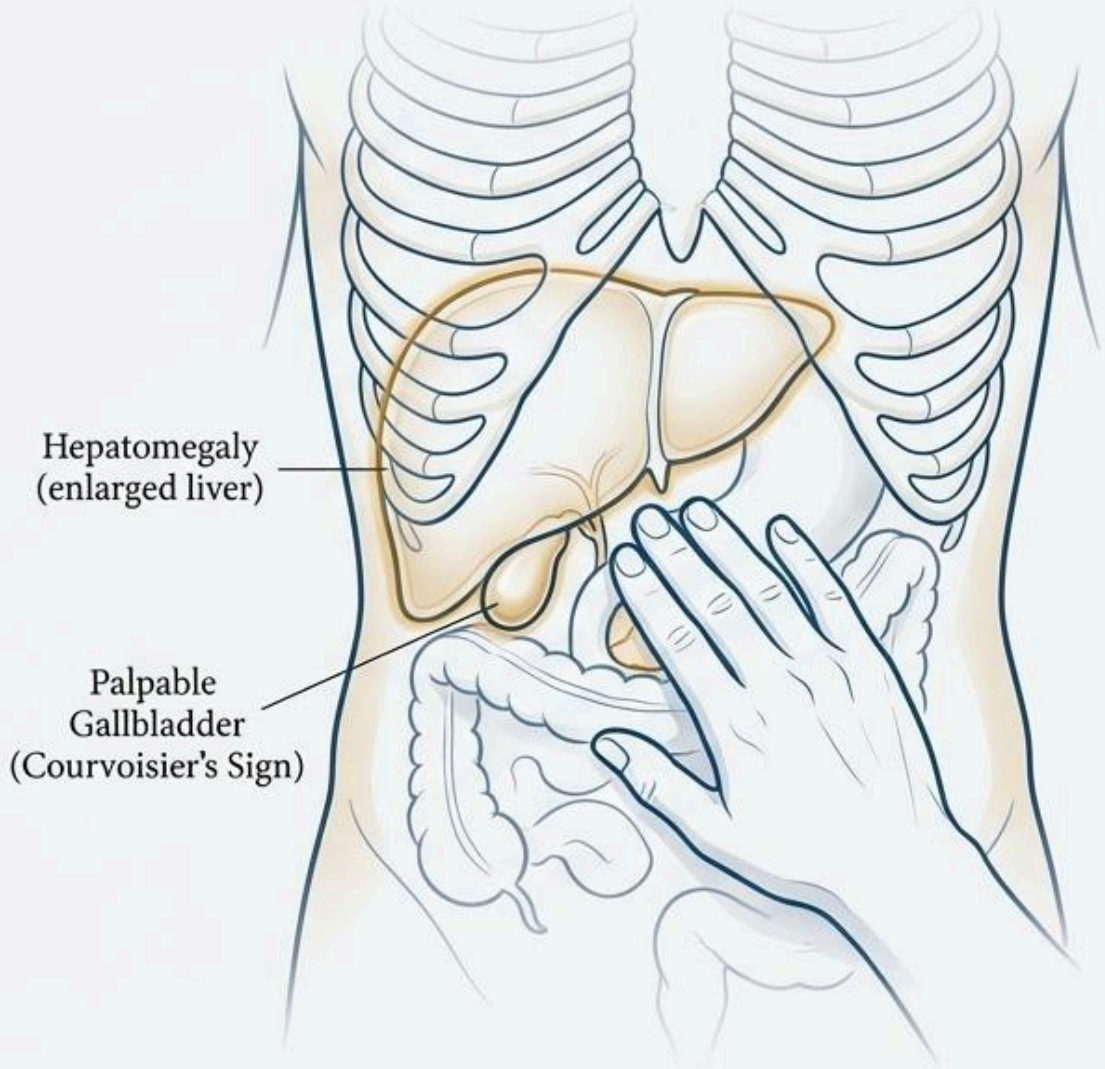
The physical examination provides objective evidence that corroborates the patient's reported symptoms and can reveal key signs of biliary obstruction and hepatomegaly.

Jaundice: Icterus (yellowing of the sclera) is the most prominent finding.

Hepatomegaly: An enlarged liver is palpable in **25 to 40%** of cases due to ductal dilation and congestion.

RUQ Tenderness or Mass: A palpable mass may be present in **10%** of patients.

Courvoisier's Sign: A palpable, non-tender gallbladder in a jaundiced patient. While a classic sign of distal obstruction (pancreatic or biliary), its diagnostic utility is limited.



Laboratory Tests Confirm the Pattern of Cholestasis

The initial laboratory workup is crucial for confirming a cholestatic pattern of liver injury, which is the biochemical signature of biliary obstruction.

Elevated Alkaline Phosphatase (ALP)

Markedly elevated, often 2 to 10 times the upper limit of normal.

Elevated Bilirubin

Total bilirubin is typically elevated, often above 10 mg/dL. The elevation is predominantly in the direct (conjugated) fraction.

Elevated Gamma-Glutamyl Transpeptidase (GGT)

Elevated GGT confirms the hepatobiliary origin of the elevated ALP.

Aminotransferases (AST/ALT): May be normal initially but can become elevated as chronic obstruction leads to hepatocellular injury.

The Role and Limitations of Tumor Marker CA 19-9

Carbohydrate Antigen 19-9 (CA 19-9) is the most established serum marker for cholangiocarcinoma, but its interpretation requires careful clinical correlation.

Diagnostic Utility

- Elevated levels support the diagnosis of cholangiocarcinoma.
- A concentration **>1000 U/mL** is highly suggestive of advanced disease.
- Can be used to monitor treatment response and detect recurrence if initially elevated.

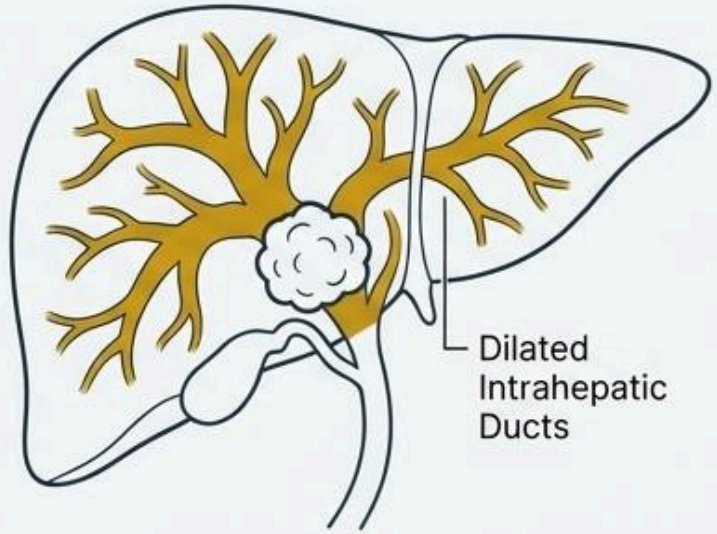
Critical Caveats

- **Low Specificity**: Frequently elevated in benign conditions, especially cholangitis and biliary obstruction. Interpret with caution in jaundiced patients.
- **Variable Sensitivity**: Ranges from 50 to 90%; a normal level does not rule out cancer.
- **Lewis Antigen Negative**: 5-10% of the population cannot produce CA 19-9, resulting in a false-negative test.

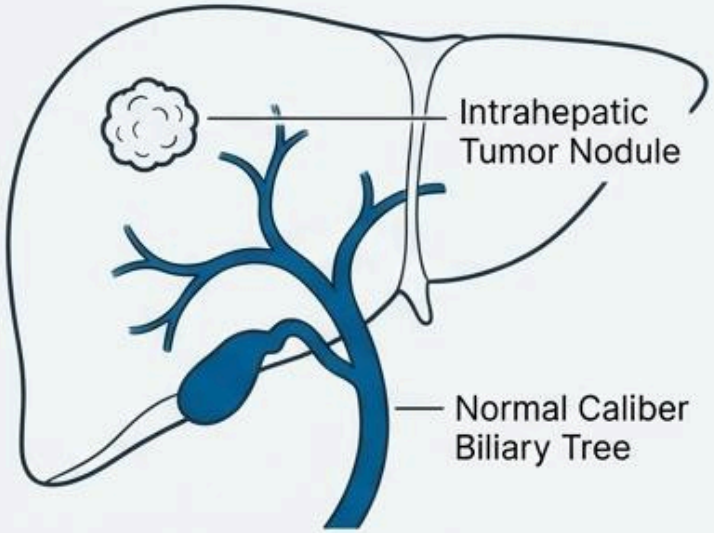
A Different Picture: The Presentation of Intrahepatic Tumors

Unlike extrahepatic tumors, intrahepatic cholangiocarcinomas (approx. 5-10% of cases) often do not obstruct the main bile ducts and therefore present differently.

Extrahepatic Obstruction



Intrahepatic Mass



Key Distinctions in Presentation

- **Jaundice is Uncommon:** Serum bilirubin is often normal or only slightly elevated.
- **Prominent ALP Elevation:** An isolated or disproportionately high alkaline phosphatase is a key laboratory clue.
- **Nonspecific Symptoms:** Patients may report vague RUQ pain, weight loss, or anorexia.
- **Incidental Discovery:** Many lesions are found incidentally on imaging performed for abnormal liver tests.

Diagnosing Cholangiocarcinoma: A Clinical Pathway

An Overview of Key Diagnostic Tools and Staging Systems

The First Clues: Clinical Presentation and Laboratory Findings

Clinical Signs & Symptoms

Biliary Obstruction: Jaundice (present in **90%** of extrahepatic cases), pruritus, clay-colored stools, and dark urine.

Constitutional Symptoms: Abdominal pain (a constant dull ache in the RUQ in **30-50%** of cases), significant weight loss (**30-50%**), and fever (up to **20%**).

Intrahepatic Distinction: Intrahepatic cholangiocarcinoma often presents without jaundice, discovered incidentally during workup for abnormal liver tests.

Key Laboratory Abnormalities

Cholestatic Pattern: Elevated total bilirubin (often >10 mg/dL), direct bilirubin, and alkaline phosphatase (usually 2- to 10-fold increase) are typical for extrahepatic tumors.

Intrahepatic Pattern: Patients usually have elevated alkaline phosphatase, while serum bilirubin is often normal or only slightly elevated.

Shining a Light: The Role of Ultrasound

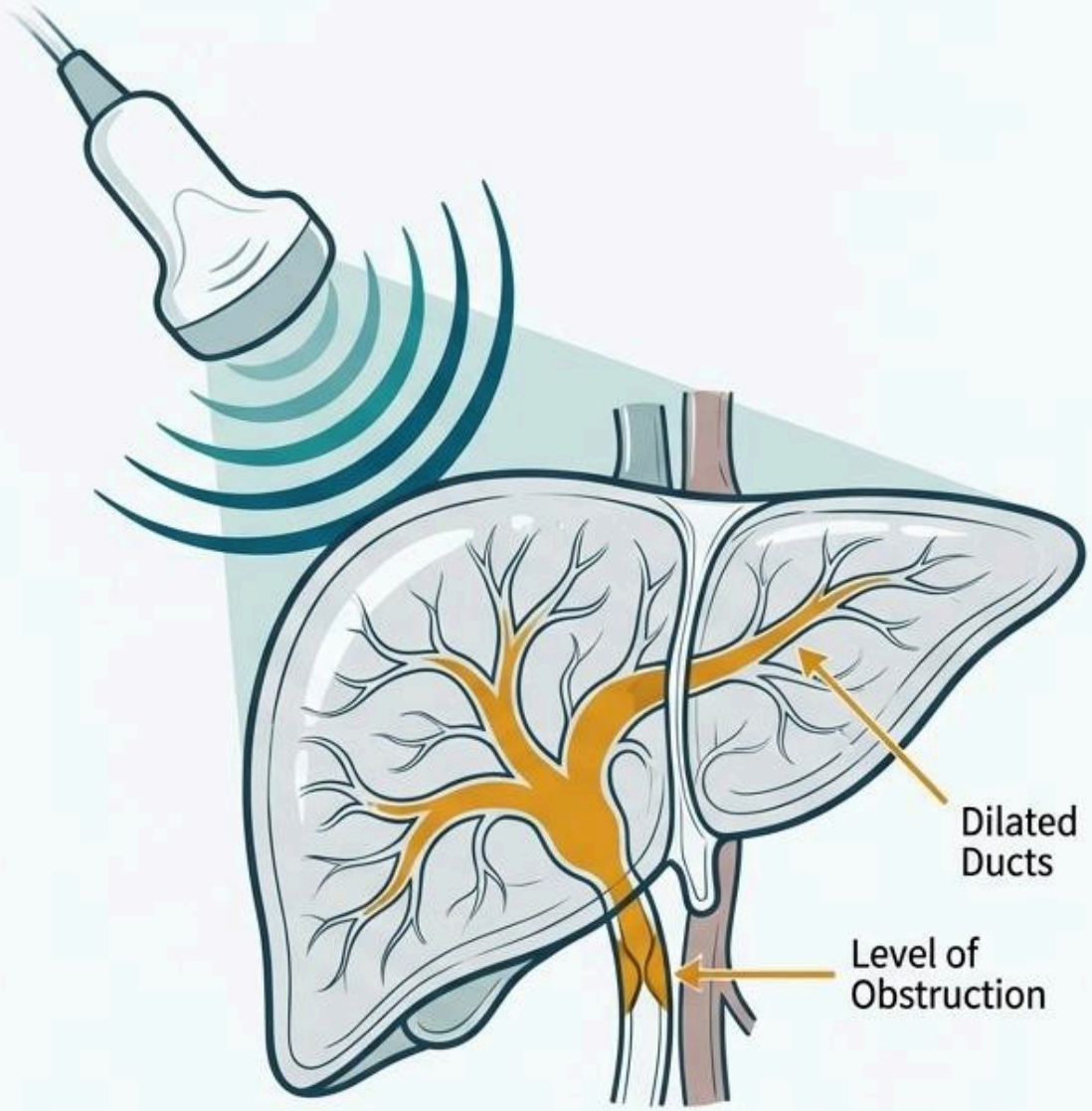
The frontline imaging study for jaundiced patients.

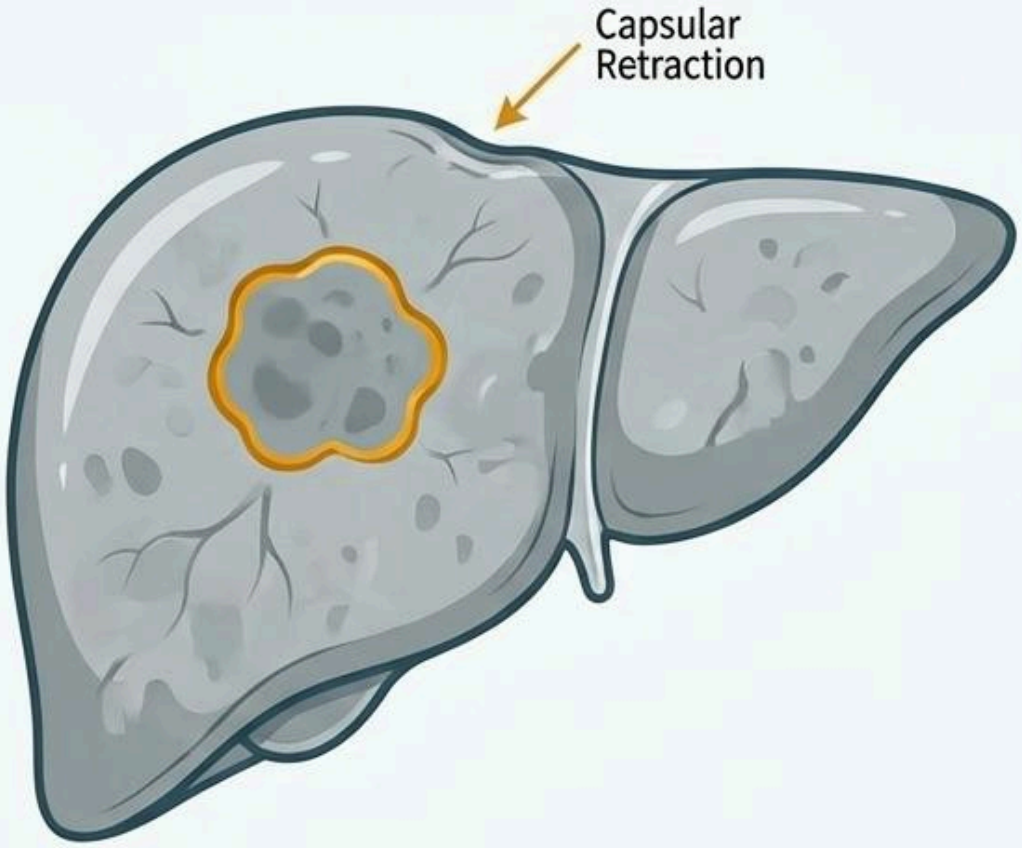
Key Findings & Utility

- **Confirms Biliary Obstruction**: Highly sensitive for detecting biliary tract dilation (>6 mm in normal adults).
- **Localizes Obstruction Level**: Can differentiate proximal (intrahepatic duct dilation only) from distal obstructions (both intra- and extrahepatic dilation).
- **Excludes Other Causes**: Effective at ruling out gallstones as the cause of obstruction.

Key Limitations

- Often unable to visualize the distal common bile duct, which may be obscured by duodenal air.
- The bile ducts may not be visibly dilated in patients with underlying primary sclerosing cholangitis (PSC) or cirrhosis.
- Duplex ultrasound is a useful adjunct to evaluate vascular involvement (portal vein, hepatic artery), a key indicator of unresectability.





A Deeper Look: Computed Tomography (CT)

A core modality for detecting masses, clarifying the level of obstruction, and staging.

Key Findings & Utility

Detects Intrahepatic Tumors: Identifies hypodense lesions, which may show peripheral rim enhancement after contrast. Capsular retraction is seen in up to 20% of cases.

Assesses Local Spread: Visualizes liver atrophy, a sign of chronic obstruction often associated with hilar tumors (e.g., dilatation of ducts in an atrophied lobe with hypertrophy of the contralateral lobe).

Identifies Metastases: Can detect distant metastases, although with limitations.

Crucial Limitations

- Low sensitivity for nodal disease; preoperative lymph node enlargement is not definitive evidence of non-curability.
- Limited ability to establish the full extent of intraductal tumor spread, particularly for the periductal infiltrative type.

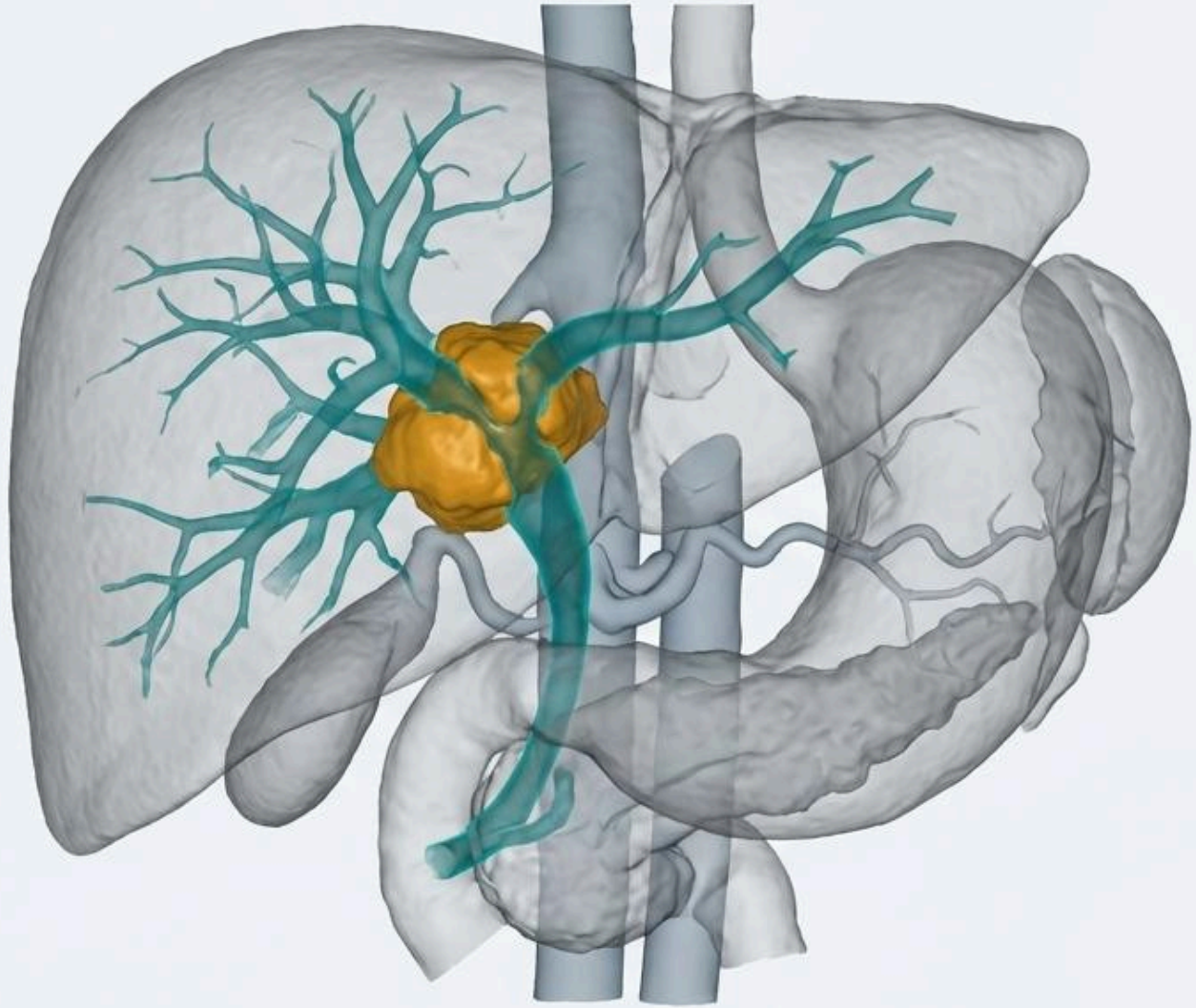
The Clearest Picture: MRI with MRCP

Primary Role:
The premier non-invasive technique for evaluating the biliary tree, particularly for assessing resectability of perihilar tumors.

Key Advantages:

- **Creates a 3D Biliary Map:** MRCP visualizes the intra- and extrahepatic bile ducts without invasive contrast, allowing assessment of the anatomy both above and below a stricture.
- **Superior Tumor Characterization:** On MRI, cholangiocarcinomas are typically hypointense on T1-weighted images and heterogeneously hyperintense on T2-weighted images. Delayed contrast images show progressive, concentric enhancement.
- **High-Quality Vascular Assessment:** Provides information on vascular involvement comparable to angiography.

Clinical Note
If possible, MRCP should be performed before biliary drainage, as a collapsed biliary tree is more difficult to evaluate.



Getting Closer: Endoscopic Tools for Diagnosis and Intervention

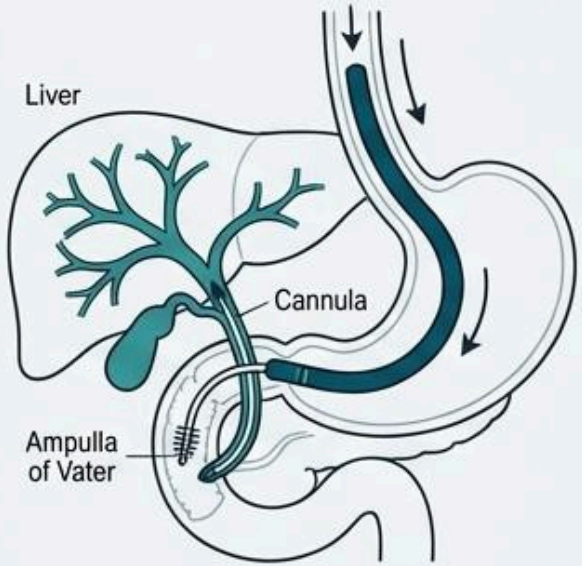
ERCP: Endoscopic Retrograde Cholangiopancreatography

Function: Direct visualization and cholangiography of the biliary tree.

Diagnostic Utility: Allows for tissue sampling via brush cytology and direct intraductal biopsy.

Therapeutic Utility: Enables placement of biliary stents to relieve obstruction and jaundice.

Risk: Injection of contrast into an obstructed system carries a risk of cholangitis, especially in hilar tumors where complete drainage can be difficult.

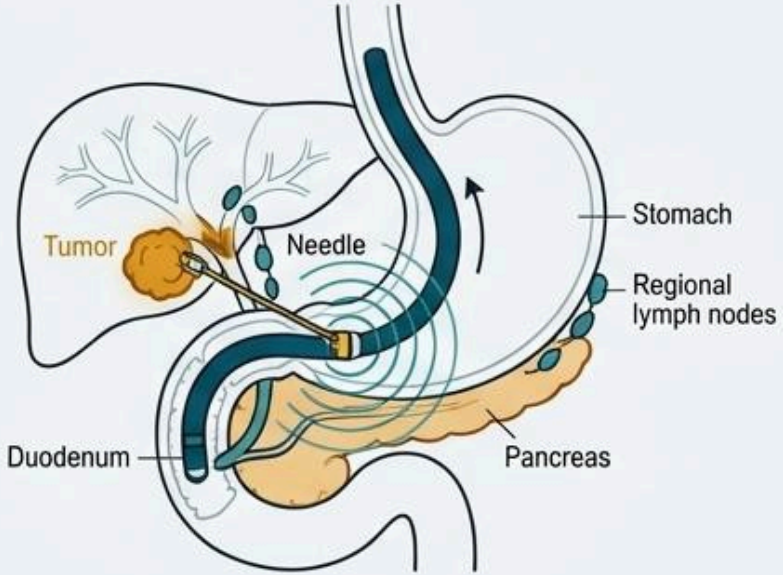


EUS: Endoscopic Ultrasound

Function: High-resolution imaging from within the stomach and duodenum.

Diagnostic Utility: Excellent for visualizing distal bile duct lesions and regional lymph nodes. Allows for EUS-guided fine-needle aspiration (FNA) of tumors and nodes.

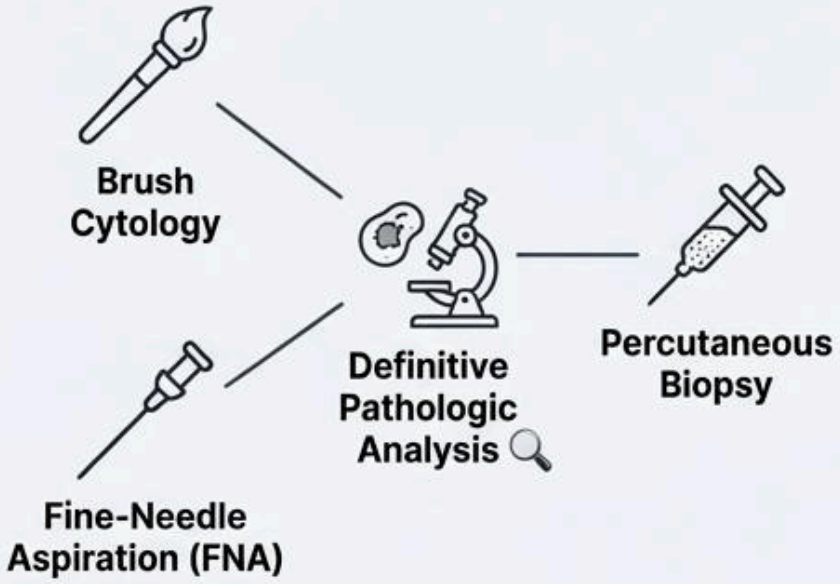
Advantage: Has a greater sensitivity for detecting malignancy in distal tumors than ERCP with brushings and avoids contrast injection into the biliary tree.



The Definitive Proof: The Role of Tissue Sampling

Methods of Acquisition

- **Brush Cytology**: Obtained during ERCP. Sensitivity is limited (35-69%), but a positive result is definitive. Combining with FISH analysis can improve sensitivity.
- **Fine-Needle Aspiration (FNA):** Typically guided by EUS for distal lesions or lymph nodes.
- **Percutaneous Biopsy:** Guided by CT or ultrasound for accessible intrahepatic mass lesions.



Is a Preoperative Tissue Diagnosis Always Necessary?

- Not always. It is not critical for potentially operable patients with characteristic imaging findings.
- It is most important when:
  - The origin of a stricture is clinically indeterminate.
  - The patient is being considered for non-operative therapy (chemotherapy/radiation).

⚠ Critical Consideration: Risk of Tumor Seeding

- FNA and percutaneous biopsies carry a rare but significant risk of seeding the needle tract with malignant cells.
- For patients with perihilar tumors who are potential liver transplant candidates, percutaneous tissue sampling should be avoided as it may preclude transplantation.

Obtaining a Tissue Diagnosis Can Be Challenging and Is Not Always Required Before Surgery

Methods of Tissue Acquisition

- **ERCP with Brush Cytology/Biopsy:** Common for extrahepatic lesions, but sensitivity is limited (35-69%).
- **EUS with Fine Needle Aspiration (FNA):** High sensitivity for distal tumors and regional nodes.
- **Percutaneous Biopsy:** CT- or MRI-guided for intrahepatic masses.

When a Biopsy is Critical

- For strictures of indeterminate origin (e.g., in PSC).
- When planning non-operative treatment like chemotherapy or radiation.
- When definitive proof of malignancy is required before proceeding with major surgery.

When to Defer or Avoid Biopsy

- **High Suspicion of Resectable Disease:** When imaging is classic and a negative biopsy would not alter the surgical plan.
- **Potential Liver Transplant Candidates:** Percutaneous biopsy is contraindicated due to the risk of tumor seeding along the needle tract, which disqualifies a patient from transplantation.

The decision to biopsy is a strategic one, balancing diagnostic certainty against the risks of a non-diagnostic result and potential tumor seeding.

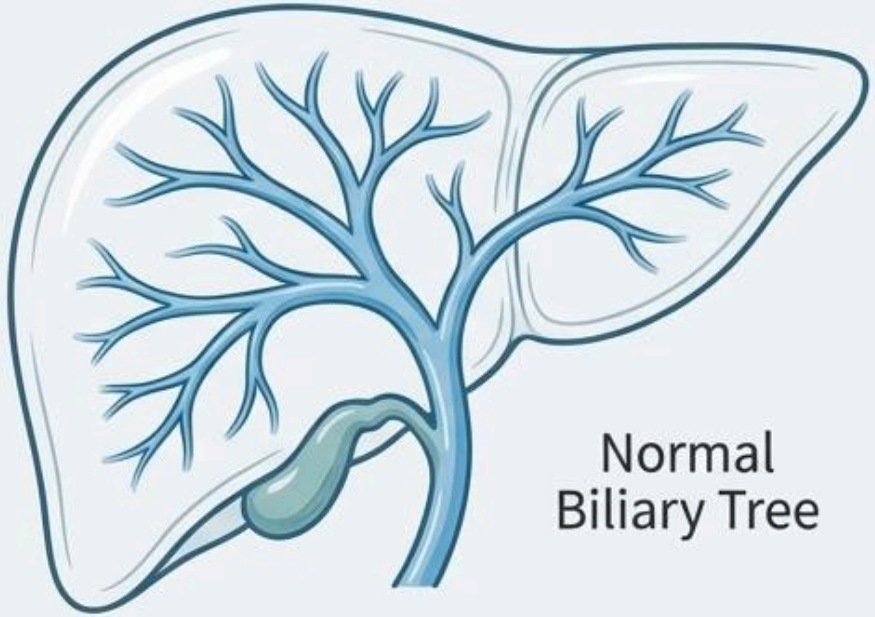
A Special Challenge: Diagnosing in Primary Sclerosing Cholangitis (PSC)

The Diagnostic Dilemma

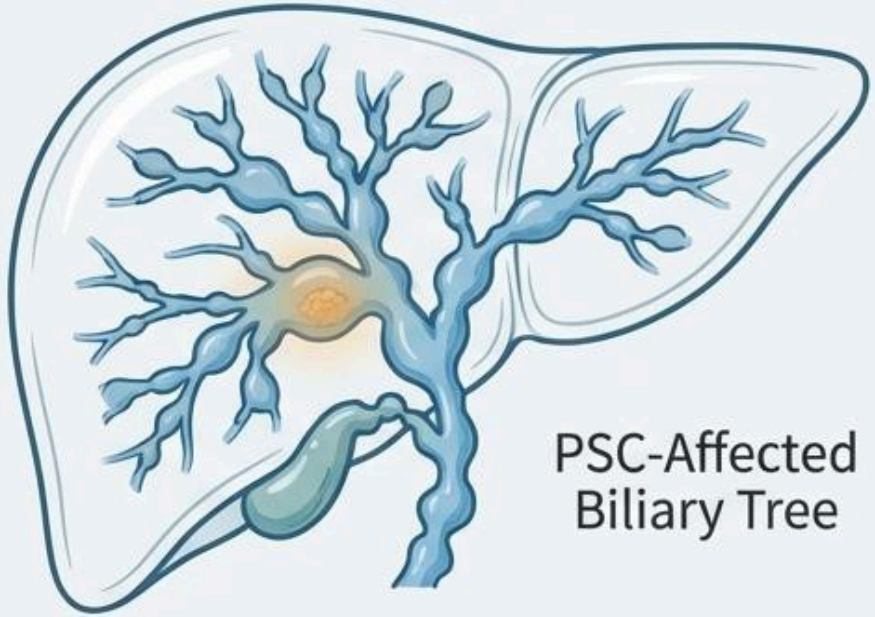
- The baseline diffusely abnormal and strictured biliary tree in PSC makes it difficult to differentiate benign dominant strictures from malignancy.
- Mass lesions are infrequently identified on imaging, and significant biliary ductal dilation may be absent.
- Abdominal lymphadenopathy is a common benign finding in PSC and does not necessarily indicate malignant involvement.

A Multi-Modal Approach is Required

- **High Index of Suspicion:** Suspect cholangiocarcinoma with rapid clinical deterioration (jaundice, weight loss) or a rising CA 19-9 level (>129 U/mL is a common threshold of suspicion).
- **Serial Imaging**
  MRCP is used to monitor for progressive stricturing or the development of a polypoid mass (≥1 cm).
- **Advanced Endoscopy**
  ERCP with brush cytology, often enhanced with FISH analysis, is used to sample dominant strictures.

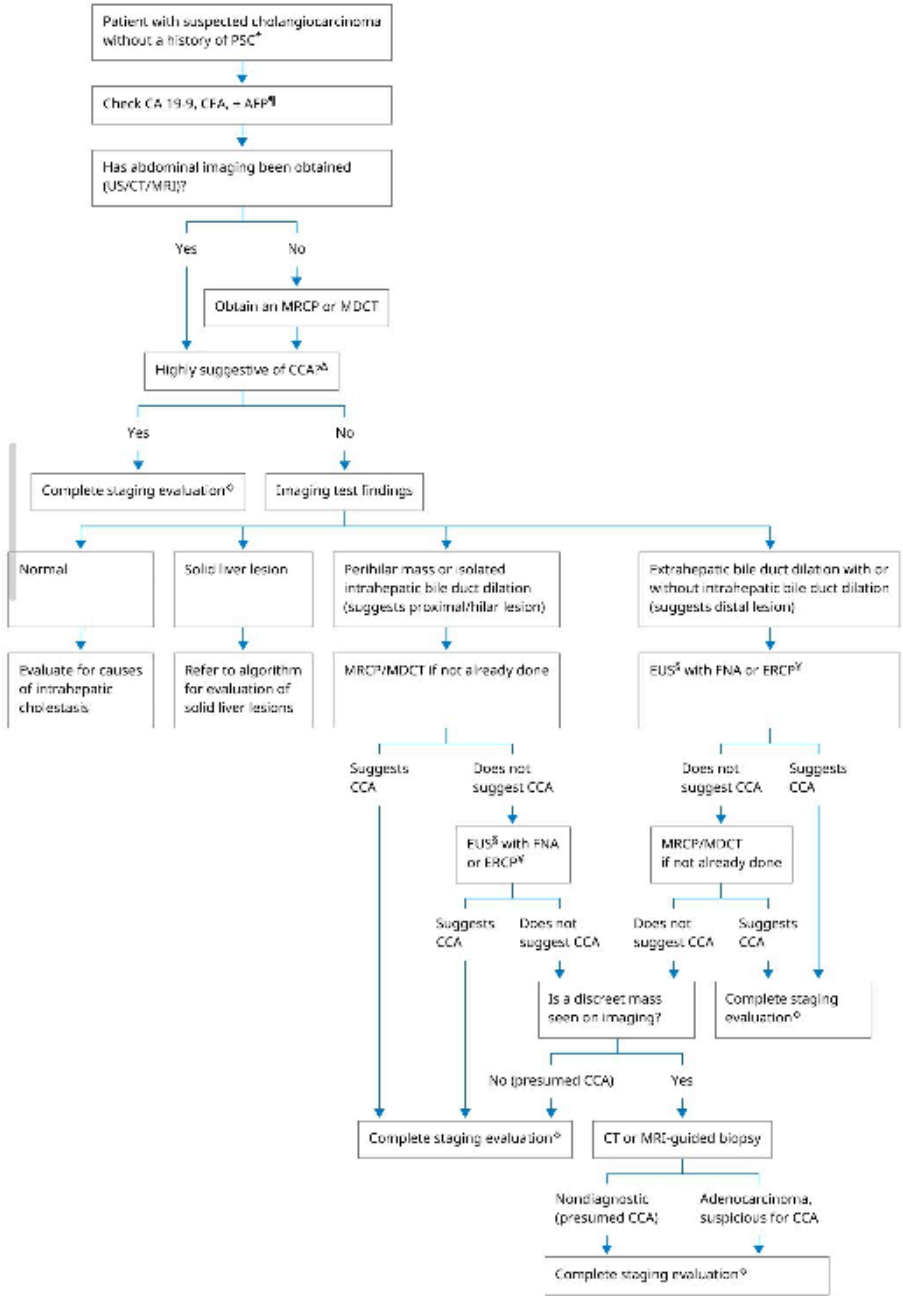


Normal
Biliary Tree

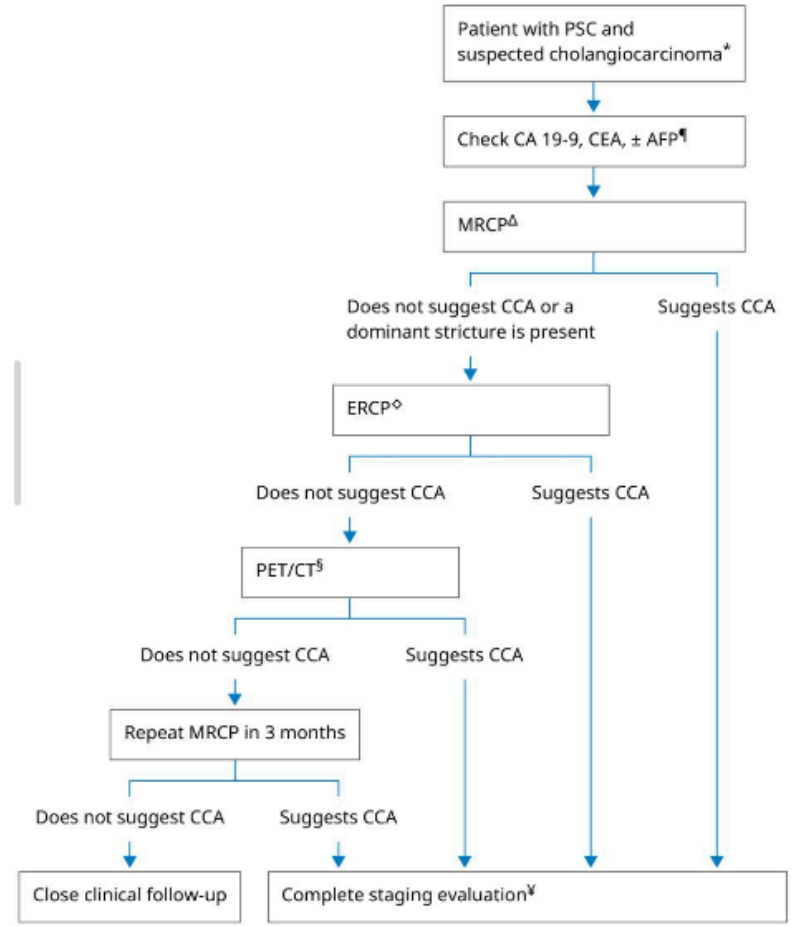


PSC-Affected
Biliary Tree

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



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



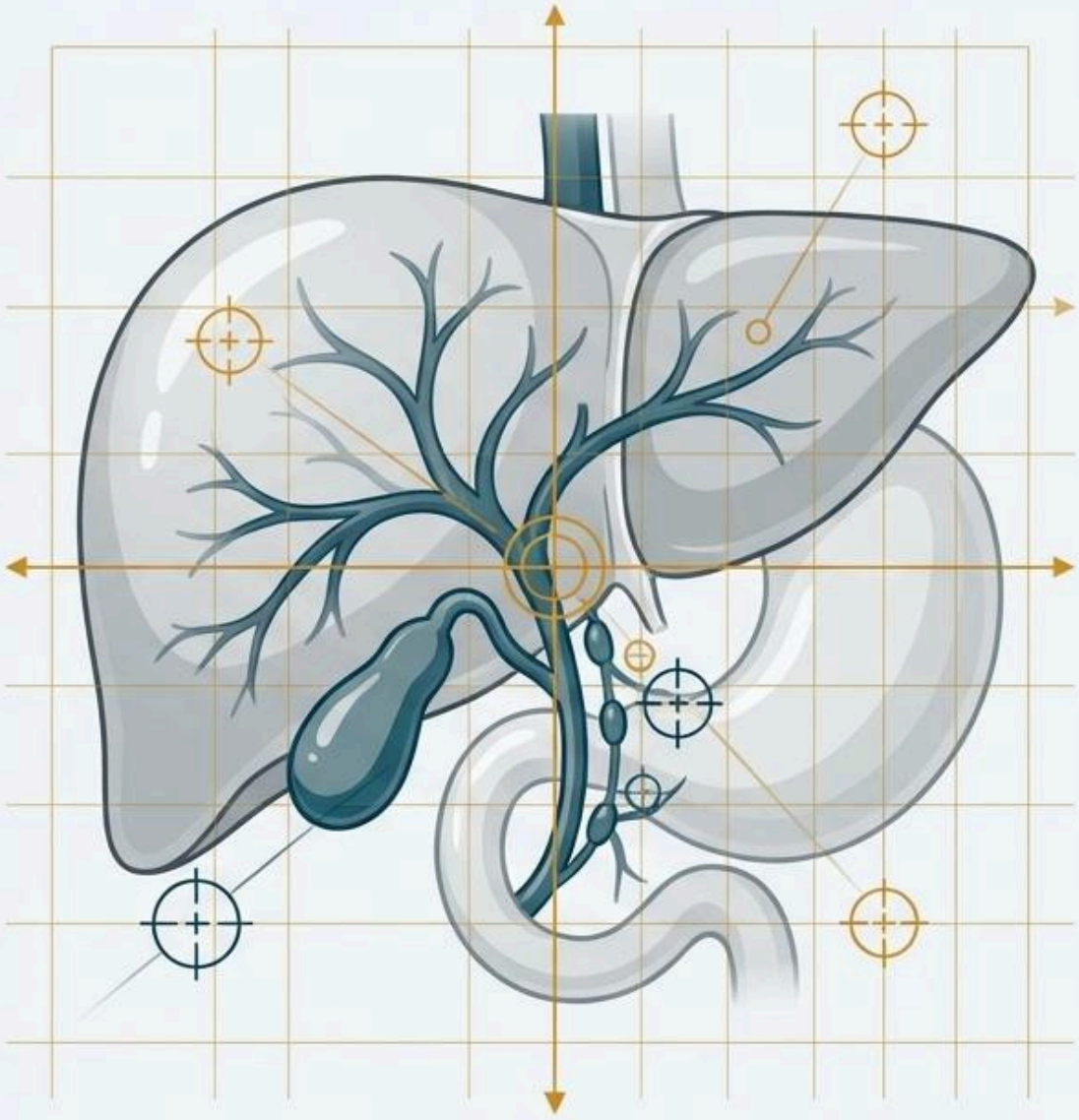
Mapping the Battlefield: Staging Cholangiocarcinoma

The Purpose of Staging

- To determine the anatomical extent of the disease.
- To assess resectability and guide the therapeutic approach (surgical vs. non-surgical).
- To provide critical prognostic information for patients.

Key Staging Questions

1. How far has the primary tumor invaded locally? (T stage)
2. Are regional lymph nodes involved? (N stage)
3. Is there evidence of distant metastatic disease? (M stage)
4. For perihilar tumors, what is the specific pattern of bile duct involvement? (Bismuth-Corlette)



The Universal Language: Understanding the TNM System

T (Tumor)

Describes the size and extent of the primary tumor. Definitions are based on factors like invasion into blood vessels or adjacent structures.

N (Nodes)

Indicates whether the cancer has spread to nearby (regional) lymph nodes. The latest
classifications are based on the *number* of involved nodes rather than their location.

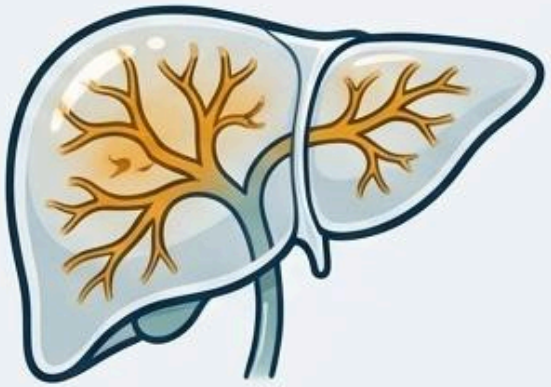
M (Metastasis)

Specifies whether the cancer has spread to distant parts of the body.

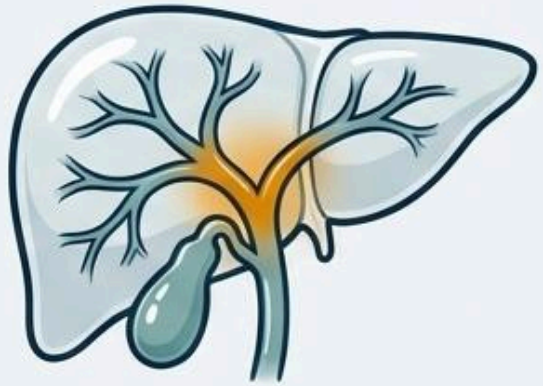
A Critical Distinction for Cholangiocarcinoma

There are **three separate TNM staging systems** reflecting the distinct anatomical location and clinical behavior of each subtype:

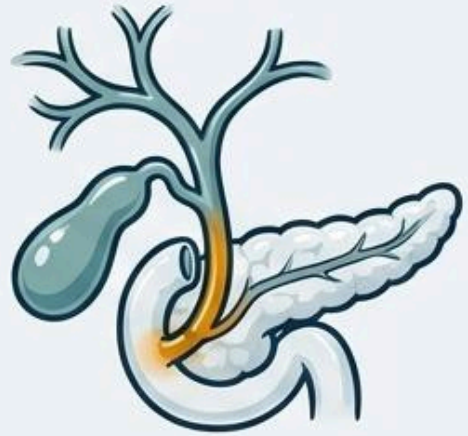
1. Intrahepatic Cholangiocarcinoma



2. Perihilar Cholangiocarcinoma



3. Distal Cholangiocarcinoma

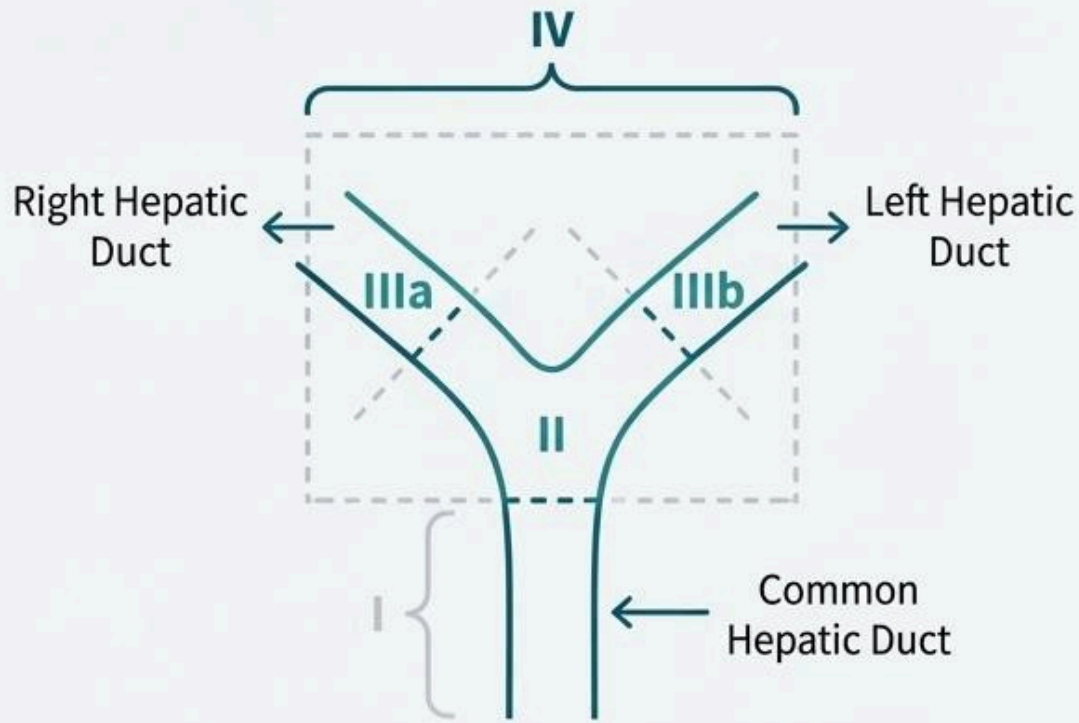


A Surgical Blueprint: The Bismuth-Corlette Classification for Perihilar Tumors

Purpose: An *anatomic* classification system that describes the extent of tumor involvement of the hepatic ducts at the hilum. It is essential for determining the surgical approach and assessing resectability.

Classification Types:

- **Type I:** Tumor is below the confluence of the left and right hepatic ducts.
- **Type II:** Tumor reaches the confluence, involving both ducts but not extending into them.
- **Type IIIa / IIIb**: Tumor occludes the common hepatic duct and extends into either the right (IIIa) or left (IIIb) hepatic duct.
- **Type IV**: Tumor is multicentric or involves the confluence and extends into **both** the right and left hepatic ducts. Type IV tumors have a higher rate of positive surgical margins.



Distal bile duct cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*/high-grade dysplasia
T1	Tumor invades the bile duct wall with a depth less than 5 mm
T2	Tumor invades the bile duct wall with a depth of 5 to 12 mm
T3	Tumor invades the bile duct wall with a depth greater than 12 mm
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery

Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes

Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

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

Perihilar bile duct cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*/high grade dysplasia
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue, or tumor invades adjacent hepatic parenchyma
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades the main portal vein or its branches bilaterally, or the common hepatic artery; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement

Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three positive lymph nodes typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreaticoduodenal, and portal vein lymph nodes
N2	Four or more positive lymph nodes from the sites described for N1

Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups			
When T is...	**And N is...**	**And M is...**	**Then the stage group is...**
Tis	N0	M0	0
T1	N0	M0	I
T2a b	N0	M0	II
T1	N0	M0	IIIA
T4	N0	M0	IIIB
Any T	N1	M0	IIIC
Any T	N2	M0	IVA
Any T	Any N	M1	IVB

Intrahepatic bile duct cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* (intraductal tumor)
T1	Solitary tumor without vascular invasion, ≤5 cm or >5 cm
T1a	Solitary tumor ≤5 cm without vascular invasion
T1b	Solitary tumor >5 cm without vascular invasion
T2	Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral peritoneum
T4	Tumor involving local extrahepatic structures by direct invasion

Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present

Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis present

Prognostic stage groups			
When T is...	**And N is...**	**And M is...**	**Then the stage group is...**
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II
T3	N0	M0	IIIA
T4	N0	M0	IIIB
Any T	N1	M0	IIIB
Any T	Any N	M1	IV

The Core Question: Determining If a Curative Resection is Possible

The primary goal of the preoperative workup is to determine resectability. While true resectability can often only be confirmed during surgical exploration, imaging provides critical guidance based on established criteria.

Resectability Checklist

General Criteria for Resectability:

- ✓ **Absence of Disseminated Disease:** No distant metastases (e.g., peritoneal, lung).
- ✓ **Absence of Distant Nodal Metastases:** Disease is confined to regional lymph nodes. Retropancreatic and paraceliac nodes are considered distant.
- ✓ **Absence of Extrahepatic Adjacent Organ Invasion:** Tumor has not spread directly into nearby organs.
- ? **Invasion of Major Blood Vessels:**
  - Traditionally a sign of unresectability.
  - However, some expert centers now perform en bloc resection with vascular reconstruction for invasion of the main portal vein or hepatic artery.

Key Caveat:

For perihilar tumors especially, surgical exploration is often necessary to definitively assess resectability when radiological studies are inconclusive.

Specific Resectability Challenges in Perihilar Tumors

Perihilar cholangiocarcinomas pose unique challenges due to their proximity to critical vascular and biliary structures. High-resolution imaging helps identify features that suggest local unresectability.

Radiographic Criteria Suggesting Unresectability:

- Bilateral hepatic duct involvement extending to the secondary biliary radicles.
- Encasement or occlusion of the main portal vein before its bifurcation.
- Atrophy of one liver lobe combined with encasement of the contralateral portal vein branch.
- Atrophy of one liver lobe combined with contralateral secondary biliary radicle involvement.
- Involvement of both the right and left hepatic arteries.

An Evolving Standard:

It is important to note that many experienced centers will now offer resection to select patients who meet some of these traditional 'unresectable' criteria, often involving complex vascular reconstruction.

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The Biliary Drainage Debate: To Stent or Not to Stent?

Whether to perform preoperative biliary drainage in jaundiced patients is controversial, with valid arguments on both sides. The decision often depends on the patient's condition, the tumor location, and the planned extent of resection.

The Case FOR Preoperative Drainage

- **Reduces Surgical Risk:** Cholestasis and liver dysfunction from unrelieved obstruction are major contributors to postoperative morbidity and mortality.
- **Improves Liver Function:** Most centers selectively drain patients with serum bilirubin >10 mg/dL, deferring surgery until levels are <3 mg/dL.
- **Prepares for Major Resection:** Routine drainage of the future liver remnant is supported if the predicted volume is less than 30%.

The Case AGAINST Routine Drainage

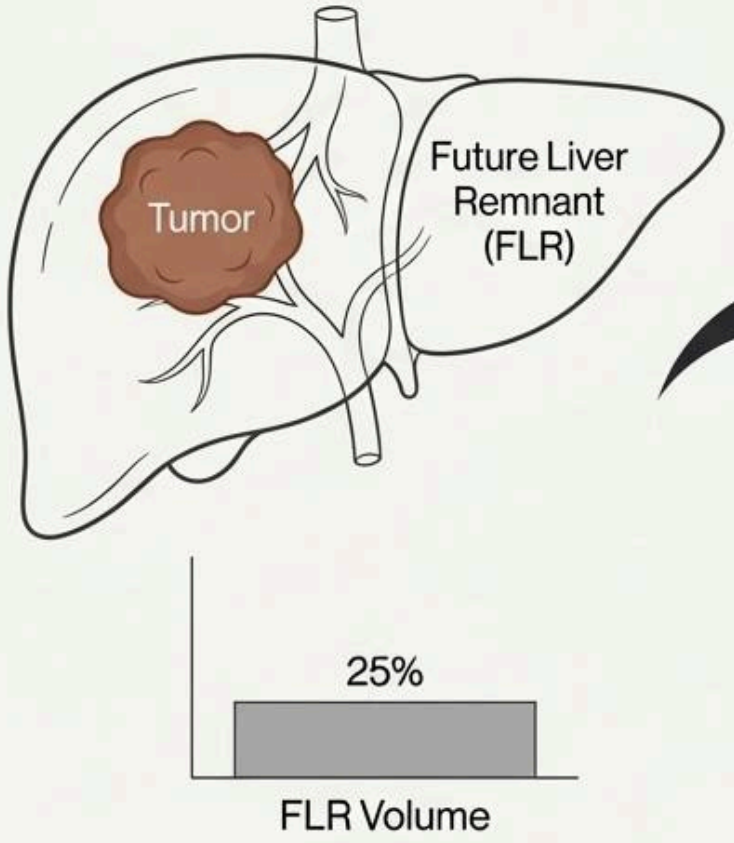
- **Increased Complications:** A meta-analysis found preoperative drainage was associated with significantly higher overall and infectious complication rates, with no difference in mortality.
- **Risk of Tumor Seeding:** Percutaneous catheter tracts have a reported recurrence rate of up to 6%, which is associated with poorer survival.
- **Imaging Artifacts:** Stents can impede radiographic assessment.

A Practical Approach: For patients with perihilar or intrahepatic tumors requiring a major liver resection, preoperative drainage of the future liver remnant is a widely accepted strategy to make surgery safer.

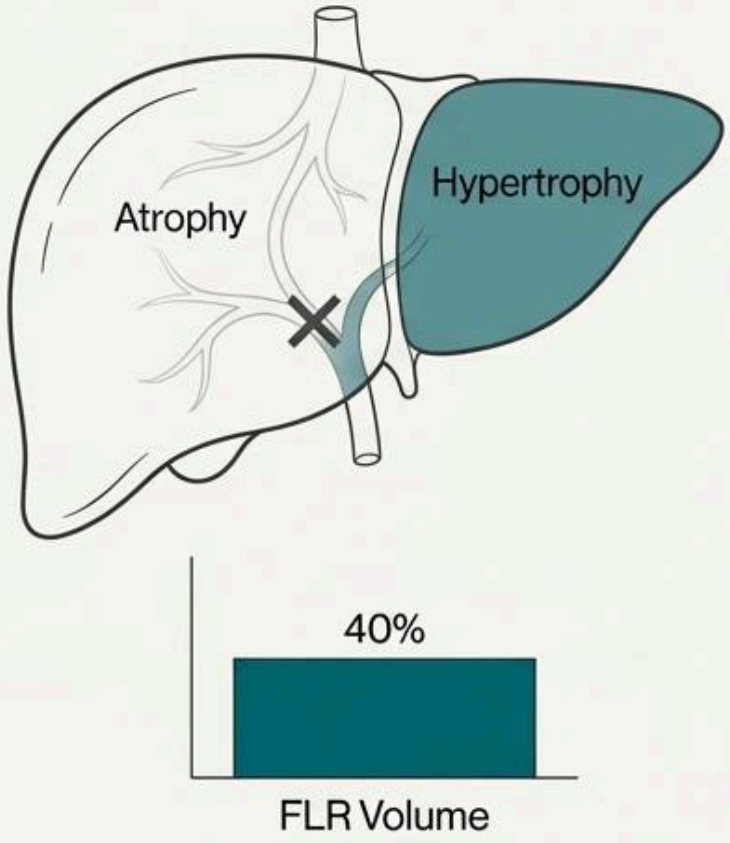
Expanding the Limits of Resection: The Role of Portal Vein Embolization

Many curative resections for cholangiocarcinoma require removing a large portion of the liver. Portal Vein Embolization (PVE) is a key preoperative strategy used to increase the size of the future liver remnant (FLR), making these extensive resections safer.

Before PVE



After PVE



The Concept:

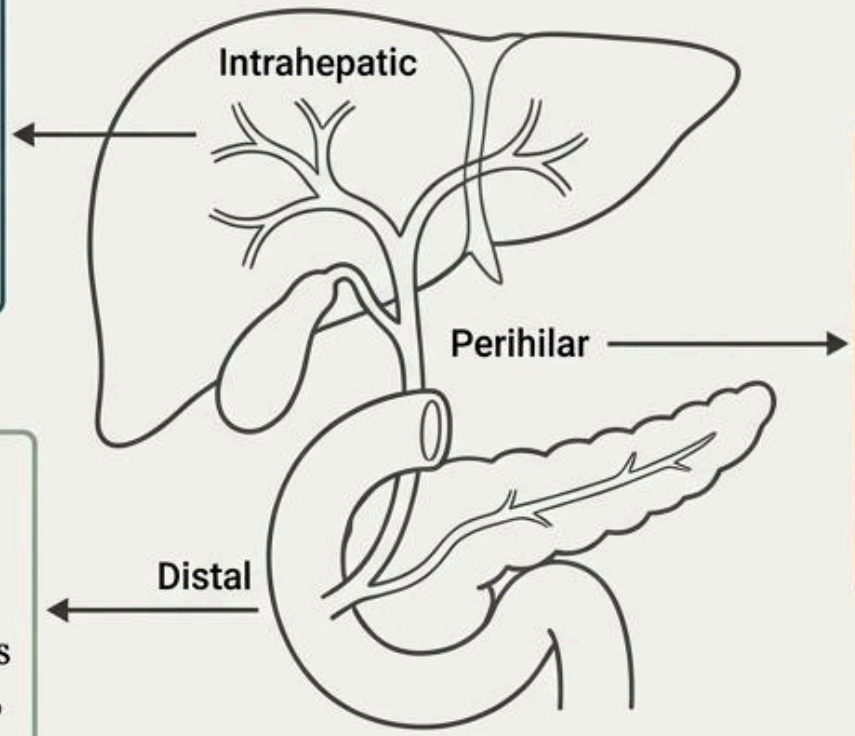
- An interventional radiologist embolizes (blocks) the portal vein branch feeding the part of the liver that contains the tumor and will be resected.
- This redirects blood flow to the non-embolized side of the liver (the FLR).
- Over several weeks, this redirection of blood flow induces compensatory hypertrophy (growth) of the FLR.
- Once the FLR reaches an adequate volume (typically >30% of total liver volume), the patient can proceed safely to surgery.

The Surgical Approach Is Highly Individualized Based on Tumor Location

Intrahepatic Cholangiocarcinoma

Procedure: Formal Hepatic Resection (Hepatectomy).

Goal: Achieve negative resection margins by removing the tumor along with a portion of the liver.



Perihilar Cholangiocarcinoma (Klatskin Tumor)

Procedure: A complex operation involving *en bloc* resection of extrahepatic bile ducts, gallbladder, and regional lymph nodes, combined with a major Hepatic Resection.

Reconstruction: Roux-en-Y hepaticojejunostomy to restore bile flow.

Distal Cholangiocarcinoma

Procedure: Pancreaticoduodenectomy (Whipple Procedure).

Rationale: The tumor's location necessitates removal of the pancreatic head, duodenum, gallbladder, and distal bile duct.

Resection of cholangiocarcinoma involves complex hepatobiliary and pancreatic surgery that should be performed at high-volume, expert centers

The Surgical Blueprint: Matching the Approach to the Tumor's Location

Surgical resection is individualized based on the tumor's location. Each anatomical site dictates a fundamentally different and highly specialized operative approach to achieve the goal of a complete, margin-negative resection.

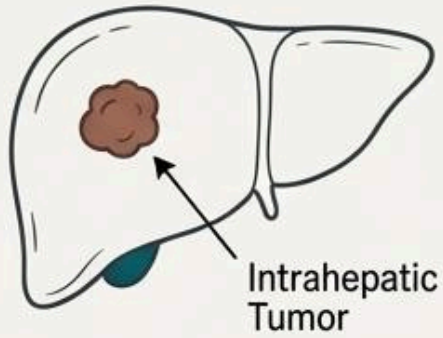
Location	Primary Surgical Approach	Core Principle
Intrahepatic 	Hepatic Resection	Removal of the tumor-bearing portion of the liver parenchyma with a clear margin of healthy tissue.
Perihilar 	Bile Duct Resection + Major Hepatic Resection	Aggressive en bloc removal of the extrahepatic bile ducts, gallbladder, and a significant portion of the liver (often including the caudate lobe) to clear the tumor at the hilum.
Distal 	Pancreaticoduodenectomy (Whipple Procedure)	Removal of the head of the pancreas, duodenum, gallbladder, and the distal portion of the common bile duct.

Surgical Strategies in Detail: Intrahepatic and Perihilar Tumors

The complexity of resection increases significantly as tumors move from within the liver parenchyma to the critical junction of the hilum.

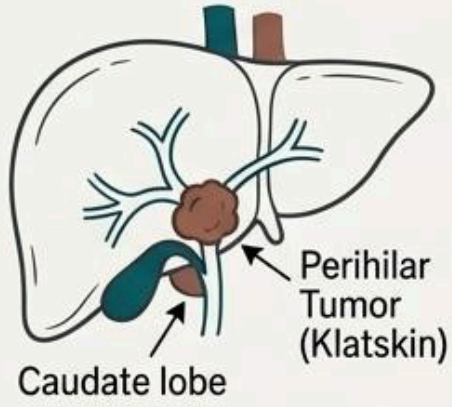
Intrahepatic Cholangiocarcinoma

- **Procedure:** Formal hepatic resection (lobectomy or segmental resection).
- **Goal:** Achieve microscopically negative resection margins (R0). Curative resection is achieved in fewer than 30% of patients.
- **Lymphadenectomy:** The role is controversial. While lymph node involvement is a powerful prognostic factor, routine portal lymph node dissection has not been proven to provide a therapeutic benefit and carries risks (e.g., common bile duct devascularization). Resection is often not pursued if grossly positive porta hepatis lymph nodes are present due to poor prognosis.



Perihilar Cholangiocarcinoma (Klatskin Tumors)

- **Challenge:** Bile duct resection alone leads to high local recurrence due to early microscopic spread into the hepatic ducts and caudate lobe branches.
- **Procedure:** An aggressive en bloc resection is the standard of care.
  - Resection of the extrahepatic bile ducts and gallbladder.
  - Major hepatic resection (lobectomy or triisectionectomy) is required to achieve negative margins.
  - Caudate lobe resection is often necessary as its ducts are frequently involved.
- **Reconstruction:** A Roux-en-Y hepaticojejunostomy is performed to restore bile flow.

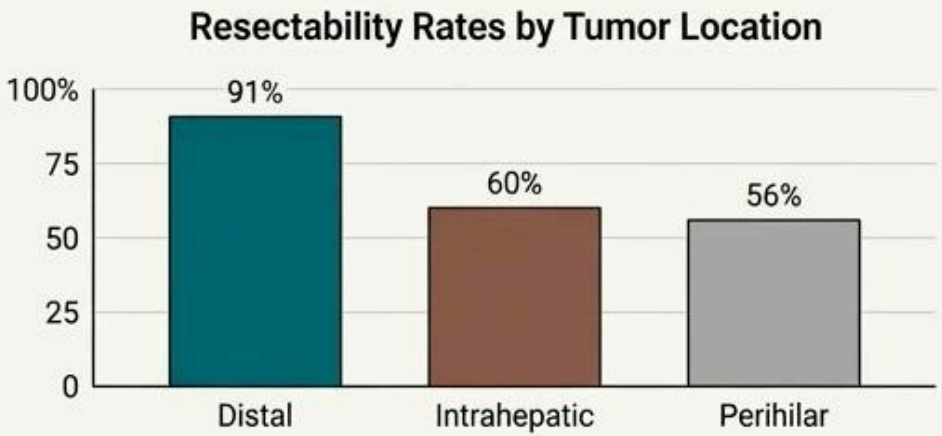


Surgical Strategy in Detail: Distal Tumors

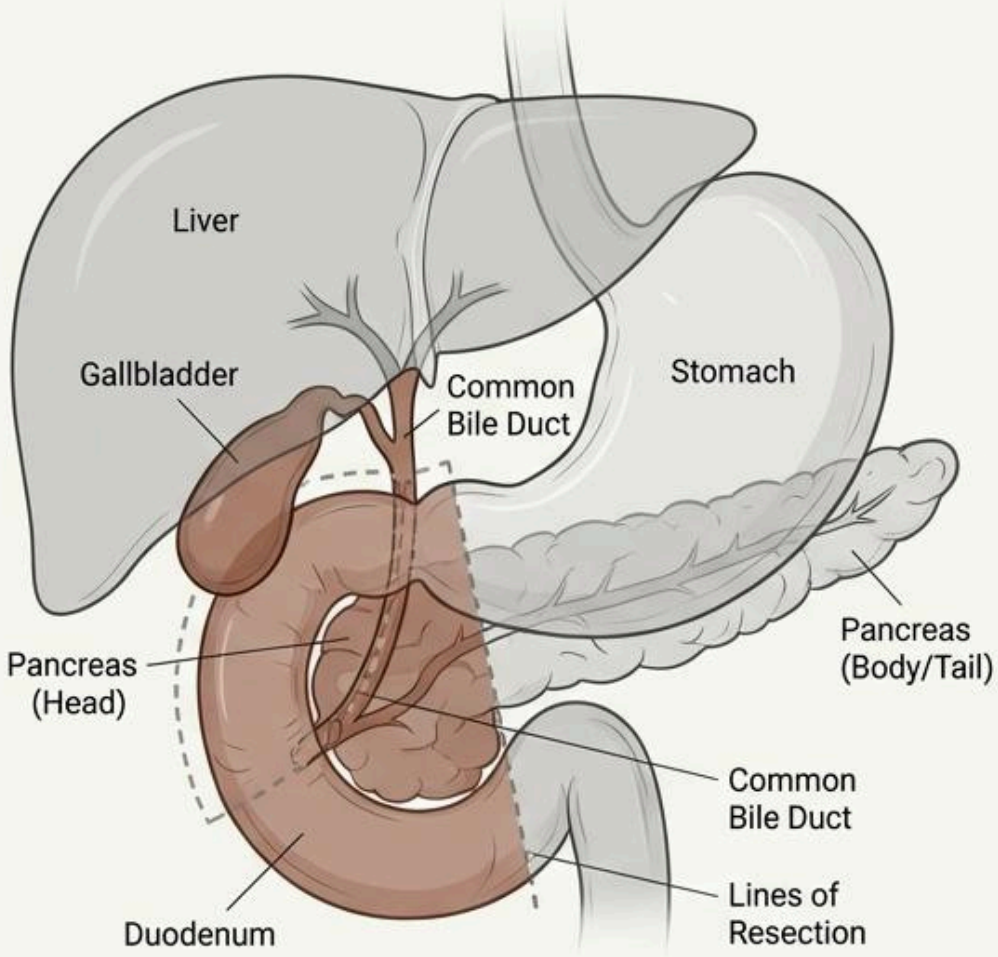
Distal cholangiocarcinomas, located in the lower portion of the bile duct near the pancreas, are treated with a well-established, major abdominal operation.

Distal Cholangiocarcinoma

- **Procedure:** Pancreaticoduodenectomy (Whipple procedure).
- **Scope:** This procedure involves the en bloc removal of:
  - The head of the pancreas
  - The duodenum
  - The gallbladder
  - The distal common bile duct
- **Resectability:** Distal tumors have the highest rate of resectability. In one large series, the resectability rates were:



- **Prognosis:** Despite higher resectability, long-term survival is still heavily dependent on achieving negative margins and the status of the lymph nodes.



The Road Ahead: The Two Most Critical Prognostic Factors

Following a potentially curative resection, long-term survival is primarily determined by two key findings from the pathology report: the status of the surgical margins and the involvement of lymph nodes.

1. Margin Status (R0 vs. R1 Resection)

Definition:

- **R0 Resection**: No cancer cells are found at the microscopic edge of the resected tissue (a "negative" or "clear" margin). This is the goal of curative surgery.
- **R1 Resection**: Microscopic cancer cells are present at the margin.

Impact: Five-year survival rates are substantially better for patients with R0 resections compared to those with R1 resections. Achieving an R0 resection is challenging, obtained in only 20-40% of proximal tumors and 50% of distal tumors in some series.

2. Lymph Node Involvement (N0 vs. N1)

Definition:

- **N0:** No cancer cells found in the regional lymph nodes.
- **N1**: Cancer cells have spread to regional lymph nodes.

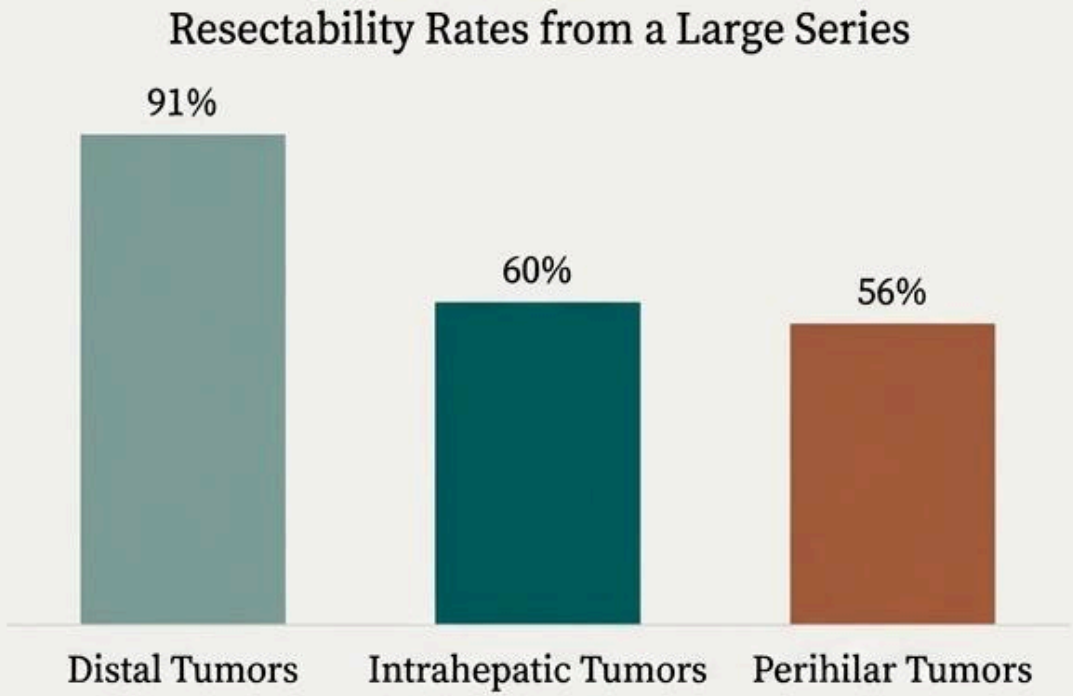
Impact: Lymph node involvement is a major negative prognostic factor.

Data Point: In a review of resected extrahepatic cholangiocarcinoma, 5-year survival was **38% for node-negative** disease versus **less than 10% for node-positive** disease.

The *number* of involved nodes also matters; survival is significantly worse for multiple nodal metastases compared to a single metastasis.

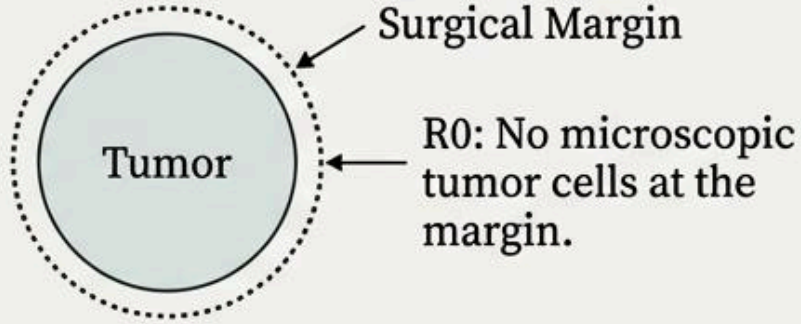
Surgical Resection Offers the Only Potential for Cure, but Is Feasible in a Minority of Patients

Resectability Varies by Location



Surgery is the cornerstone of treatment for localized disease, but most patients present at a stage that is not resectable.

The Challenge of Negative Margins (R0 Resection)



Even among resected patients, achieving a microscopically complete (R0) resection is difficult.

- Proximal Tumors (Perihilar/Intrahepatic): R0 margins obtained in only 20% to 40% of cases.
- Distal Tumors: R0 margins obtained in approximately 50% of cases.

True resectability is often determined only at the time of surgical exploration, as imaging can underestimate vascular involvement.

Adjuvant Therapy Is Recommended for High-Risk Patients to Reduce the High Rate of Recurrence

Following complete resection, disease recurrence is common. Adjuvant therapy aims aims to eradicate microscopic residual disease.

- **Extrahepatic CCA:** Relapse is most often local.
- **Intrahepatic CCA:** Recurrence can be intrahepatic, nodal, or distant.

The main risk factors for recurrence are:

- **Positive Resection Margins (R1)**
- **Lymph Node Involvement (N+)**

Based on ASCO/NCCN Guidelines, all patients with resected disease should be considered for adjuvant therapy.

- **Chemotherapy Alone:** For many patients, six months of **Capecitabine** is recommended, based on the landmark BILCAP trial.
- **Chemoradiotherapy (CRT):** For patients with **extrahepatic cholangiocarcinoma and positive margins (R1),** CRT may be offered in addition to systemic chemotherapy.

Adjuvant therapy is a critical component of the curative-intent strategy.

CLINICAL MASTERCLASS

First-Line Systemic Therapy for Advanced Disease Has Evolved to Chemoimmunotherapy

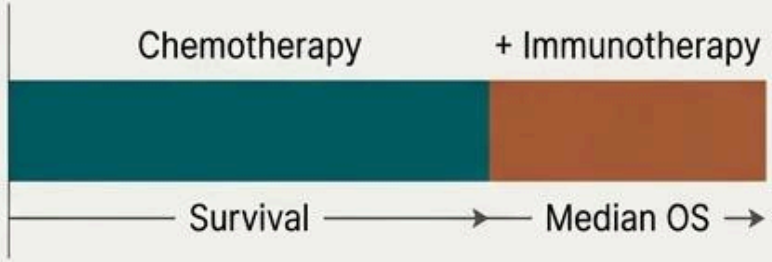
Chemotherapy Alone

Gemcitabine + Cisplatin (GemCis)

~11.7 months
median OS

Chemoimmunotherapy

Gemcitabine + Cisplatin + Immune Checkpoint Inhibitor



~12.9 months
median OS

Durvalumab + GemCis (TOPAZ-1 Trial): Median OS 12.9 months
Pembrolizumab + GemCis (KEYNOTE-966 Trial): Median OS 12.7 months

Mechanism Note: The combination is thought to enhance the anti-tumor immune response, leading to a modest but statistically significant survival benefit.

Key Takeaway: The addition of immunotherapy represents the new first-line standard of care for patients with advanced cholangiocarcinoma.

Beyond Chemotherapy: Molecularly Targeted Therapies Are Transforming Treatment for a Subset of Patients

Next-Generation Sequencing (NGS) of tumor tissue is now essential for all patients with advanced disease to identify actionable molecular alterations, which are particularly common in intrahepatic cholangiocarcinoma.

FGFR2 Fusions/ Rearrangements

~15-20% of iCCA

Pemigatinib, Futibatinib

IDH1 Mutations

~20% of iCCA

Ivosidenib

BRAF V600E Mutation

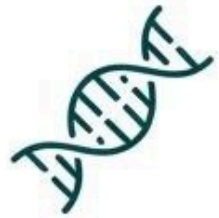
~5% of biliary tract cancers

Dabrafenib + Trametinib

HER2 Amplification/ Overexpression

~5-20% (enriched in extrahepatic)

Trastuzumab-based combinations, Zanidatamab



dMMR/MSI-High

~3% of CCA

Pembrolizumab

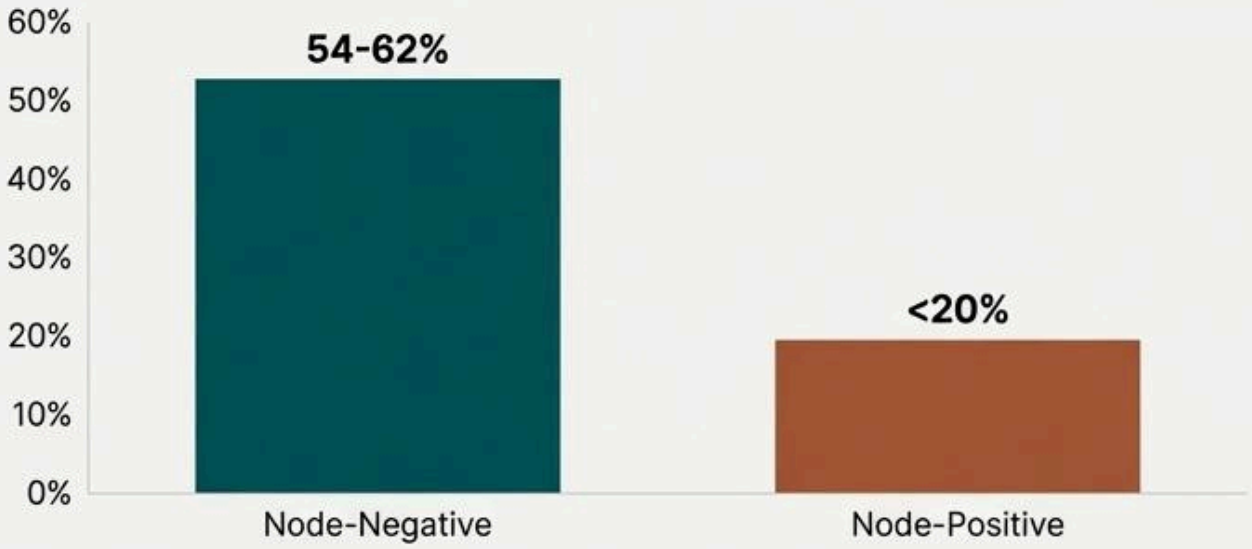
Key Takeaway: Precision medicine is no longer investigational; it is a standard of care that offers significant and durable responses for patients with the right molecular profile.

Prognosis Remains Challenging and Is Primarily Driven by Nodal Status and Margin-Negative Resection

Key Prognostic Factors in Resectable Disease

1. **Lymph Node Status:** The single most important factor. The presence of nodal metastases dramatically worsens outcomes.
2. **Resection Margin Status:** Achieving a microscopically negative (R0) resection is crucial for long-term survival.

5-Year Survival in Resected Distal CCA by Nodal Status



Overall Prognosis

Cholangiocarcinoma has a poor overall prognosis, with an average five-year survival rate of 5 to 10 percent for node-positive disease across modern series.

A Concluding Perspective

While the prognosis for cholangiocarcinoma remains guarded, significant progress has been made.

The path forward lies in:

- **Earlier detection** strategies.
- **Aggressive multimodality treatment** for localized disease (surgery + adjuvant therapy).
- The continued **expansion of molecularly targeted therapies** for advanced disease.