PRACTICAL INSIGHTS FOR EARLY DIAGNOSIS AND MANAGEMENT OF BILIARY TRACT CANCERS

Differential Diagnosis: Biliary Tract Cancer vs. Other Hepatobiliary Diseases

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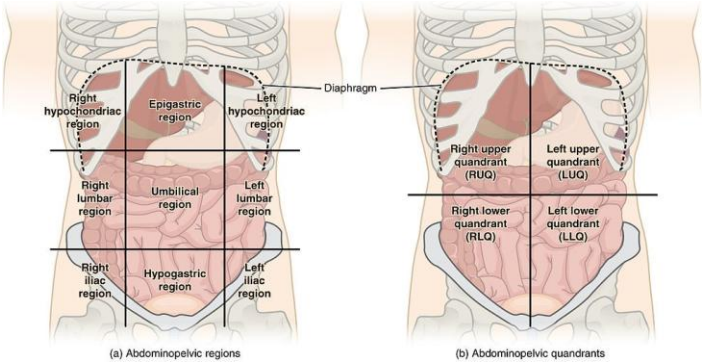
Key Diseases in the Differential Diagnosis

	Clinical features	How to Differentiate from Biliary Tract Cancer
Hepatocellular Carcinoma (HCC)	Arises in cirrhotic liver, RUQ mass, ↑AFP	HCC shows **arterial enhancement with venous washout** on CT/MRI; typically, in cirrhotics
Liver Metastases	Often asymptomatic, multiple lesions, known primary	**Multiple hypo- or hypervascular lesions**; biopsy or known malignancy history confirms
Biliary Tract Cancer/Cholangitis (Acute)	Charcot's triad: fever, RUQ pain, jaundice	Acute onset; responds to antibiotics; no mass; ERCP may show pus and obstruction
Gallstones/Cholecystitis	RUQ pain, postprandial symptoms, fever	Ultrasound shows gallstones; no mass; resolves with cholecystectomy
Choledocholithiasis	Jaundice, biliary colic, sometimes cholangitis	Stone visible on imaging; ERCP can confirm and treat; no tissue mass
Primary Sclerosing Cholangitis (PSC)	Younger male, IBD association, cholestatic LFTs	**Beaded appearance** of bile ducts on MRCP; may coexist with cancer (especially CCA)
Pancreatic Head Cancer	Painless jaundice, weight loss, Courvoisier's sign	Mass in pancreas on CT/MRI; can compress CBD causing similar presentation
Benign Biliary Stricture	History of surgery, trauma, pancreatitis	Smooth, short stricture; lacks mass or constitutional symptoms



RUQ: Right Upper Quadrant; **AFP:** Alpha-FetoProtein; **IBD**: Inflammatory Bowel Disease; **LFTs**: Liver Function Test; **CT**: Computed Tomography; **MRI**: Magnetic Resonance Imagin; **ERCP**: Endoscopy Retrograde CholangioPancreatography; **MRCP**: Magnetic Resonace CholangioPancreatography; **CCA**: Cholangiocarcinoma.

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Biomarkers and Pathological Findings

	Biliary Tract Cancer	Others
CA 19-9	often elevated (>100–1000+ U/mL), +++cholangiocarcinoma	Mildly elevated in inflammation (e.g., cholangitis, PSC)
CEA	Sometimes elevated	Non-specific
AFP	Normal in biliary cancer	↑ in HCC
Liver Function Test	Cholestatic pattern (↑ALP, ↑GGT, ↑bilirubin)	Present in all obstructive or cholestatic diseases
Biopsy/Cytology	Adenocarcinoma cells, glandular formation, perineural invasion	Inflammatory or reactive changes in benign disease
ERCP brushings	Positive in ~50% of cholangiocarcinoma cases	May be false-negative; repeat
Targetable genetic alterations	FGFR2 fusion, IDH1 mutation, HER2 amplification, MSI-H, BRAFV600E, NRTK and RET fusions	—

CA 19-9: Cancer Antigen 19-9**; PSC:** Primary Sclerosing Cholangitis**; CEA:** Carcinoembryonic Antigen; **AFP:** Alpha-FetoProtein; **HCC**: HepatoCellular Carcinoma; **ALP:** Alkaline Phosphatase; **GGT**: Gamma-Glutamyl Transferase; **ERCP**: Endoscopy Retrograde CholangioPancreatography; **FGFR2**: Fibroblast Growth Factor Receptor 2; **IDH1**: Isocitrate DeHydrogenase 1; **HER2**: Human Epidermal Growth Receptor 2; **MSI-H**: Microsatellite Instability-High; **BRAF V600E**: Mutation; **NTRK**: Nuerotrophic Tyrosine Receptor Kinase; **RET**: Rearranged Euring Transfection

Banales JM, Marín JJG, Lamarca A, Rodrigues PM, Khan SA, Roberts LR, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol. 2020 Sep;17(9):557–88. doi: 10.1038/s41575-020-0310-z.

Role of Imaging in Differentiation

	Findings in Biliary Tract Cancer	How it Helps
Ultrasound (US)	Biliary dilation; mass may be missed unless advanced	Good first-line; detects obstruction, stones
CT Scan	Mass with delayed enhancement, biliary dilation, liver capsular retraction	Evaluates extent, nodes, vasculature
MRI / MRCP	Ductal irregularities, mass lesions, periductal infiltration	Best for ductal anatomy, staging, PSC vs. CCA
ERCP	Stricture seen, allows brushings or stent	Diagnostic and therapeutic
PET-CT	May detect metastases or recurrence	Not always reliable in mucinous tumors
Contrast-enhanced MRI (liver-specific agents)	Distinguishes HCC (arterial phase enhancement) from cholangiocarcinoma	Especially helpful for intrahepatic lesions

CT: Computed Tomography; **MRI**: Magnetic Resonance Imagin; **MRCP**: Magnetic Resonace CholangioPancreatography; **PSC**: Primary Sclerosing Cholangitis; **CCA**: Cholangiocarcinoma; **ERCP**: Endoscopy Retrograde CholangioPancreatography; **PET**: Positron Emission Tomography.

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Diagnostic Pitfalls

Pitfall	Explanation	Avoidance Strategy
Mistaking cholangitis for malignancy	Inflammatory strictures can mimic cancer on imaging	Reimage after treating infection; use ERCP brushings + cytology
Overreliance on CA 19-9	Elevated in benign obstruction or infection	Interpret in context; repeat after biliary decompression
Missing distal cholangiocarcinoma	May resemble pancreatic cancer or be missed on US	Use CT/MRI pancreas protocol + endoscopic ultrasound (EUS)
False negatives on brush cytology	Sensitivity ~50%; cancer may be missed	Consider repeat ERCP or EUS-guided biopsy; use FISH or NGS panels if available
Assuming multiple liver lesions = metastasis	Intrahepatic cholangiocarcinoma can be multifocal	Biopsy and correlate with clinical context and markers

CA 19-9: Cancer Antigen 19-9; **CT**: Computed Tomography; **MRI**: Magnetic Resonance Imagin; **ERCP**: Endoscopy Retrograde CholangioPancreatography; **FISH**: Fluorescence In Situ Hybridization; **NGS:** Next Generation Sequencing

Content created by the author. Adapted from: Saluja SS, Sharma R, Pal S, Sahni P, Chattopadhyay TK. Differentiation between benign and malignant hilar obstructions using laboratory and radiological investigations: a prospective study. HPB (Oxford). 2007;9(5):373-82. doi: 10.1080/13651820701504207. PMID: 18345322; PMCID: PMC2225516.

Conclusions and Key messages

Feature	Biliary Tract Cancer	Benign /Other Diseases
Onset	Insidious, progressive	Often acute or intermittent
Jaundice	Common, persistent	Intermittent or with fever
Mass	Present (CT/MRI)	Absent (unless inflammatory phlegmon)
Tumor markers	CA 19-9 ↑; AFP normal	AFP ↑ in HCC; CA 19-9 mild in infection
Imaging	Irregular strictures, delayed enhancement	Smooth strictures, stones, beading (PSC)
Biopsy	Malignant glandular cells	Benign, inflammatory, reactive

CT: Computed Tomography; **MRI**: Magnetic Resonance Imagin; **CA 19-9:** Cancer Antigen 19-9**; AFP:** Alpha-FetoProtein; **HCC**: HepatoCellular Carcinoma; **PSC:** Primary Sclerosing Cholangitis

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