Klatskin tumors and other cholangiocarcinoma: Diagnosis and assessment of resectability

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Agenda

- Index patient
- DDx of painless jaundice
- Review of biliary anatomy
- DDx of biliary obstruction
- Cholangiocarcinoma
  - Epidemiology and risk factors
  - Clinical manifestations
  - Classification
  - Resectability
- Companion patients
Index Patient: KR

- 53M presented to PCP with painless jaundice
- ROS: Nausea, diarrhea, 20lb weight loss over last two months, dark urine, mild pruritus
- PE: jaundice, sublingual and scleral icterus, epigastric tenderness to palpation, no HSM
- Labs: Tbili: 23.8 (direct 19.4), AP 494, ALT 50, AST 90
Differential Diagnosis: Painless Jaundice

Hyperbilirubinemia

Unconjugated hyperbilirubinemia
- Increased bilirubin production (i.e. hemolysis)
- Impaired hepatic bilirubin uptake (i.e. Gilbert’s)
- Impaired bilirubin conjugation (i.e. Crigler-Najjar)

Conjugated Hyperbilirubinemia
- Hepatocellular injury/ Intrahepatic cholestasis (i.e. viral hepatitis)
- Biliary Obstruction
Patient KR: Conjugated Hyperbilirubinemia

- Jaundice is physical manifestation of hyperbilirubinemia greater than 2mg/dL.
- Conjugated bilirubin (direct bilirubin) has already been filtered from the bloodstream into hepatocytes and conjugated to glucuronic acid.
- Our patient had a conjugated hyperbilirubinemia (his direct bilirubin was markedly elevated and constituted a large portion of his total bilirubin).
- Conjugated hyperbilirubinemia is due to either hepatocellular injury (preventing excretion of bilirubin from hepatocytes into the biliary system), or biliary obstruction (obstructing flow of bile into the GI tract). Thus, conjugated bilirubin builds up and backs into the bloodstream.
Patient KR: Likely Biliary Obstruction

- Our patient also had a markedly elevated alkaline phosphatase (AP), but only a mildly elevated AST and ALT
  - AP is made by the canilicular cells lining the biliary ducts
  - AST and ALT are made by hepatocytes

- A markedly elevated AP, relative to AST and ALT, implies that the site of injury is in the biliary ducts

- Thus, we can infer that our patient likely has a biliary obstruction leading to jaundice
Review of Biliary Anatomy

Plate 260, Netter’s Atlas of Human Anatomy 4th Ed.

Beaumont Hospitals.
https://www.beaumonthospitals.com/health-library/P07694
Menu of Radiologic Tests for Work-up of Biliary Obstruction

- Ultrasound (US)
  - Transabdominal (TA US)
  - Endoscopic (EUS)
- Computed Tomography (CT)
- Endoscopic Retrograde Cholangiopancreatography (ERCP)
- Magnetic Resonance Imaging (MRI)
- Magnetic Resonance Cholangiopancreatography (MRCP)
Patient KR: Biliary Dilatation on RUQ US

- **TA US:**
  - Bile ducts appear as tubular, branching lucencies
  - Moderate intrahepatic ductal dilation
  - No evidence of choledocholithiasis
  - Not sensitive in the diagnosis of distal CBD stones due to gas in duodenum

- Dilated bile ducts signify distal biliary obstruction

TA US, sagittal, patient KR
Image Source: BIDMC (PACS)
DDx of Biliary Obstruction

- Choledocholithiasis
- Tumors (i.e. cholangiocarcinoma)
- Primary sclerosing cholangitis
- AIDS cholangiopathy
- Acute and chronic pancreatitis
- Benign strictures (after invasive procedures)
- Parasitic infections (*Ascaris lumbricoides*, liver flukes)
Patient KR: Hilar Stricture on ERCP

- Irregular appearance of intrahepatic bile ducts consistent with non-specific cholangitis
- Marked dilation of intrahepatic biliary ducts (L>R)
- Hilar stricture with narrowing of common, right and left hepatic ducts
- Pattern of stricture is highly suspicious for cholangiocarcinoma
- A stent was placed in the CBD to facilitate biliary drainage, and bile duct brushings were obtained and sent to pathology

ERCP, patient KR
Image Source: BIDMC (PACS)
Patient KR: Soft Tissue and Lymph Node Necrosis on C+ CT

- Triple phase imaging is important because cholangiocarcinoma has slow wash out in delayed phase due to dense, fibrous stroma
- Ill-defined, low attenuation, soft-tissue around the porta hepatis, consistent with tumor growth
- Low attenuation mass between IVC and portal vein, consistent with necrotic lymph node

C+ CT, axial, arterial phase, patient KR
Image Source: BIDMC (PACS)
Patient KR: Bile Duct Dilatation and Liver Metastasis on C+ CT

- Moderate intrahepatic bile duct dilatation
- Metastasis to liver

C+ CT, axial, delayed phase, patient KR
Image Source: BIDMC (PACS)
Patient KR: Tumor Invasion into Cystic Duct on C+ CT

- Soft tissue in distal cystic duct
  - Cystic duct should appear low attenuation when filled with bile, similar to adjacent gallbladder
  - In this picture, cystic duct appears distended and high in attenuation
  - Stent in CBD

- Biopsy-proven diagnosis (from ERCP): adenocarcinoma, likely of biliary origin
  - Klatskin cholangiocarcinoma

C+ CT, axial, delayed phase, patient KR
Image Source: BIDMC (PACS)
Cholangiocarcinoma: Pathogenesis and Epidemiology

- Bile duct cancer arising in the intrahepatic, perihilar, or distal biliary tree, exclusive of gallbladder and ampulla of Vater
- Originate from epithelial cells of biliary duct
- 90% adenocarcinoma, 10% squamous cell carcinoma
- Highly lethal: often locally advanced at presentation
- 5-year-survival rate: 5-10%
- In US, 1-2 cases per 100,000 population, but incidence is rising (possible detection bias)
Risk Factors

- Primary sclerosing cholangitis
  - Lifetime risk: 10-15%
  - Average age at time of diagnosis: 30s-50s
- Fibropolycystic liver disease
  - i.e. Caroli’s syndrome, congenital hepatic fibrosis, choledochal cysts
  - Lifetime risk: 15%
  - Average age at time of diagnosis: 30s-50s
- Parasitic Infection
  - Liver flukes of Clonorchis and Opisthorchis genera (from undercooked fish)
- Cholelithiasis and haptolithiasis
- Toxic exposure
  - Thorotrast
- Lynch syndrome and biliary papillomatosis
- Chronic liver disease
- Viral hepatitis
Common Clinical Manifestations

- **Symptoms:**
  - Pruritus (66%)
  - RUQ pain (30-50%)
  - Weight loss (30-50%)
  - Fever (20%)
  - Acholic stools; dark urine
  - Cholangitis (rare)

- **Physical Signs:**
  - Jaundice (90%)
  - Hepatomegaly (25-40%)
  - RUQ mass (10%)
  - Courvoisier’s sign (rare)
**Tumor Classification**

- **Intrahepatic (Peripheral):** small intrahepatic ductules (5-10%)
- **Hilar:** extrahepatic ductules (including confluence) up to point where common bile duct lies posterior to duodenum (60-70%)
  - Klatskin: involving confluence of left and right hepatic ducts
- **Extrahepatic (Distal):** originate in extrahepatic biliary duct after CBD travels posterior to duodenum (20-30%)

Nat Clin Pract Gastroenterol Hepatol 3: 33–42 doi:10.1038/ncpgasthep0389*
Bismuth-Corlette Classification

- Hilar cholangiocarcinomas are further sub-classified based on the specific ducts involved
  - Type I
  - Type II
  - Type IIIa
  - Type IIIb
  - Type IV

- Type IV is important because it involves both left and right hepatic ducts and therefore is unresectable.

# TNM Tumor Staging

<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th>Stage I: T1</th>
<th>N0</th>
<th>M0</th>
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<tr>
<td>Stage II:</td>
<td>T2</td>
<td>N0</td>
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<tr>
<td>Stage IIIA:</td>
<td>T3</td>
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<tr>
<td>Stage IIIB:</td>
<td>T4</td>
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<td>Stage IIIC:</td>
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<td>Stage IV:</td>
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- **T0**: No evidence of primary tumor
- **T1**: Solitary tumor w/o vascular invasion
- **T2**: Solitary tumor with vascular invasion, or multiple tumors <5cm
- **T3**: Multiple tumors >5cm or tumor involving major branch of portal or hepatic veins
- **T4**: Tumors with direct invasion of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum

- **N0**: No regional lymph node metastasis
- **N1**: Regional lymph node metastasis
- **M0**: No distant metastasis
- **M1**: Distant metastasis
Surgical resection is the only curative method for cholangiocarcinoma.

Unfortunately, at the time of presentation, most patients have locally advanced disease that is not surgically resectable.

Criteria for surgical resectability are based on anatomical structures involved in tumor growth.
Radiologic Assessment of Surgical Resectability: Criteria for Resectability

- Radiologic assessment begins with a pre-operative CT
  - Limited sensitivity; can establish resectability in only 60% of cases

- Tumors are NOT resectable if:
  - Retropancreatic and paraceliac nodal metastases
  - Liver metastases
  - Invasion of portal vein, main hepatic artery, or proximal branches
  - Extrahepatic organ invasion
  - Disseminated disease
Criteria for Resectability of Hilar Tumors

Hilar tumors are NOT resectable if:

- Bilateral hepatic duct involvement up to second radicles bilaterally (Bismuth IV)
- Encasement/occlusion of main portal vein proximal to its bifurcation
- Atrophy of one liver lobe with encasement of contralateral portal vein branch
- Atrophy of one liver lobe with contralateral secondary biliary radicle involvement
- Involvement of bilateral hepatic arteries
Surgical Exploration: Ultimate Determination of Resectability

- Resectability is ultimately determined at time of surgery
  - If pre-operative CT demonstrates unresectable disease, patient may receive palliative medical management or palliative surgery (biliary-enteric bypass to alleviate obstruction)
  - In all other cases, patient will undergo surgical exploration to determine resectability
    - If the tumor is resectable, it will be resected
    - If tumor is deemed unresectable after exploration, surgeon may perform a palliative bypass to alleviate obstruction

- Intra-operative US may be used intra-operatively assess depth of tumor invasion and aid in surgical decision-making
Example of Unresectable Tumor: Celiac Invasion

- Companion Patient 1: MB
- Invasion of celiac artery
  - Infiltrative soft tissue mass extending along the celiac axis

C+ CT, axial, delayed phase, patient MB
Image Source: BIDMC (PACS)
Example of Unresectable Tumor: Liver Metastasis

- Index patient: KR
- Liver Metastasis

C+ CT, axial, delayed phase, patient KR
Image Source: BIDMC (PACS)
Discussion of Companion Patients
Companion Patient 2: Central Necrosis on C+ CT

- 79F with 6 week history of mid-epigastric pain and jaundice
- C+ CT Abdomen
  - 6.6 x 6.2cm mass with peripheral enhancement in arterial phase
  - Central necrosis

C+ CT, axial, arterial phase, patient DM
Image Source: BIDMC (PACS)
Patient 2: Hyper-enhancement on Delayed Images

Area of peripheral enhancement in arterial phase, with progressive central hyper-enhancement in venous phase and marked, progressive central enhancement in delayed phase (10-minute-delay).

C+ CT, axial, triple phase, patient DM
Image Source: BIDMC (PACS)
Patient 2: Fibrotic Tumor on C+ CT

- Mass with an irregular margin, suggestive of a fibrotic tumor

C+ CT, axial, delayed phase, patient DM
Image Source: BIDMC (PACS)
Patient 2: Gallbladder Wall Invasion on C+ CT

- Hyperenhancing nodule by gallbladder signifying invasion of gallbladder wall
- Biopsy-proven diagnosis: adenocarcinoma
  - Intrahepatic Cholangiocarcinoma
Companion Patient 3: Biliary Dilatation and CHD Stricture on HASTE MRI

- 67M with 3 week history of jaundice, pruritus and weight loss
- OSH scans: dilated bile ducts and CBD strictures consistent with cholangiocarcinoma
- MRA to assess resectability:
  - Marked bilateral, intrahepatic ductal dilation to porta hepatitis
  - 3 cm common hepatic duct stricture

MRI, coronal, HASTE, patient HK
Image Source: BIDMC (PACS)
Patient 3: Liver Metastasis on HASTE MRI

- Low signal area near gallbladder fundus
- Signifies metastasis
- Tumor is unresectable

MRI, coronal, HASTE, patient HK
Image Source: BIDMC (PACS)
Patient 3: Dilated Bile Ducts and CHD Stricture on MRCP

- Dilated intrahepatic bile ducts
- Long CHD stricture extending to CBD
- Incidental finding: Pancreatic cysts (IPMT)
- Biopsy-proven diagnosis: adenocarcinoma
  - Klatskin cholangiocarcinoma

MRCP, patient HK
Image Source: BIDMC (PACS)
Cholangiocarcinoma can be a challenging radiographic diagnosis, and an even more challenging cancer to treat.

3 classifications of cholangiocarcinoma:
- Intrahepatic
- Hilar (including Klatskin)
- Extrahepatic

Hilar cholangiocarcinomas are further subclassified based on specific ductal involvement, by the Bismuth-Corlette classification system.
Summary (2)

- Many radiographic modalities are important in the diagnosis of cholangiocarcinoma
  - US, CT, ERCP, MRCP, MRI
- Radiology is helpful in determining surgical resectability, and can influence surgical management
References


- Chowdhury NR and Chowdhury JR. Diagnostic approach to the patient with jaundice or asymptomatic hyperbilirubinemia. *UpToDate*; retrieved February 2009. [http://utdol.com](http://utdol.com)


Acknowledgements

- A special thank you to: Aarti Sekhar, MD
- Gillian Lieberman, MD
- Ivan Pedrosa, MD
- Iva Petkovska, MD
- Charles Vollmer, MD
- Maria Levantakis
- Larry Barbaras