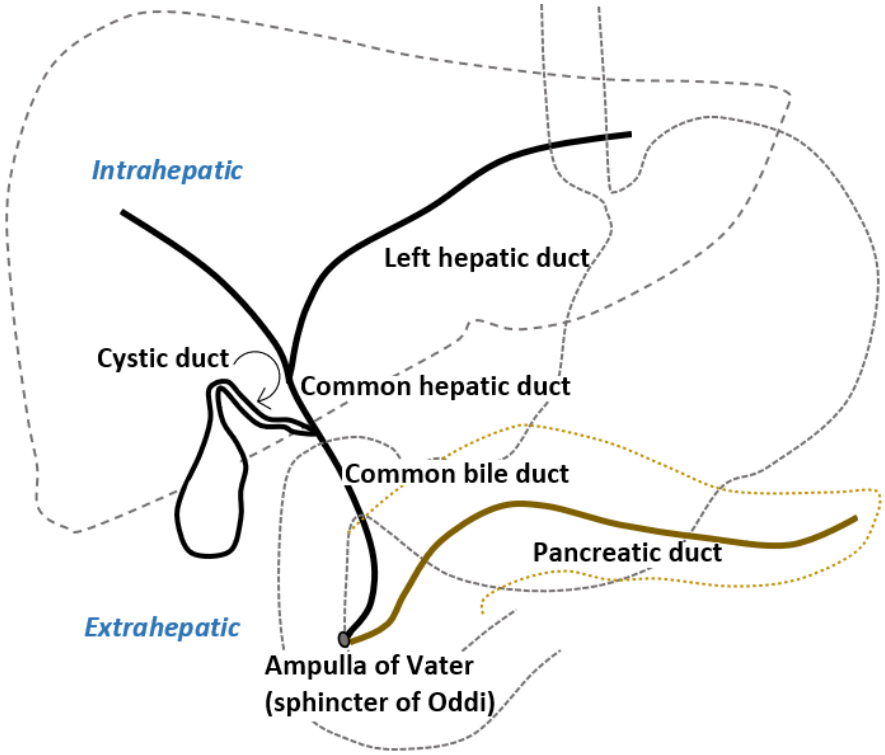
GI: Gallbladder and biliary tree

Structure and function

- The gallbladder concentrates and stores the bile produced in the liver.
    - It is poorly understood how the bile accumulates in the gallbladder. The process is usually described as “sipping”.
    - The gallbladder stores most the body’s bile in the morning and expels it in the morning with the first food which stimulates the release of cholecystokinin (**CCK**) from the enteroendocrine cells (aka I cells) of the duodenum. CCK also relaxes the sphincter of Oddi and increase bile acid secretion by the liver.



The Biliary tree

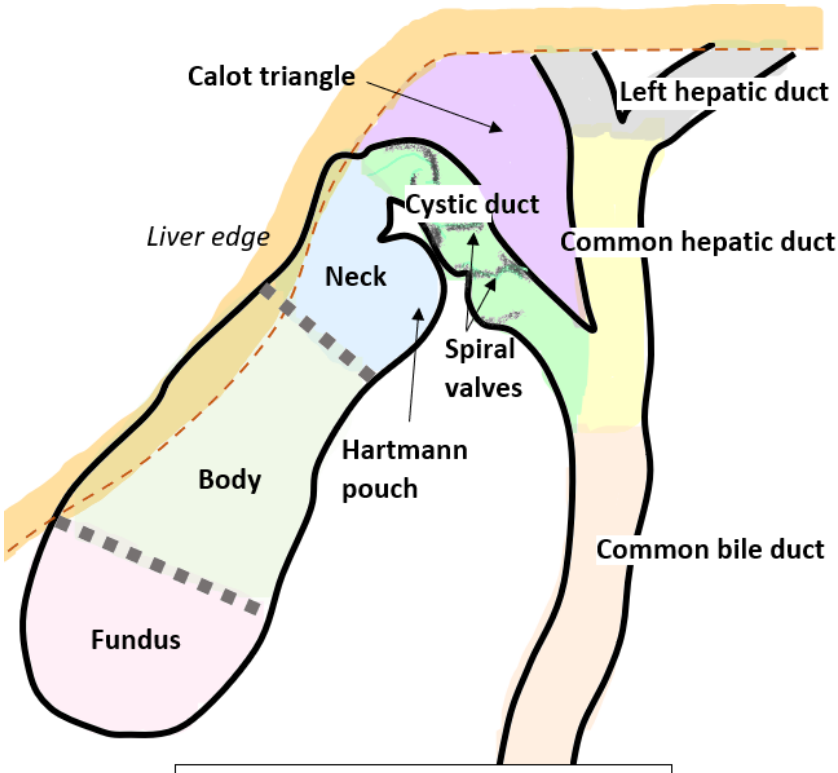
- The biliary tract starts with a tube formed from hepatocytes (bile canaliculi) with the first lining epithelial cells at the canals of Hering. These flow into the bile ductules which eventually form the left and right hepatic ducts. These fuse at the porta hepatis to form the common hepatic duct. The common bile duct is formed after fusion with the cystic duct of the gallbladder.
    - The ampulla of Vater is the narrowest point of the extrahepatic ducts and is a common place to find common bile duct gallstones.
    - The fusion of the left and right hepatic ducts is the most common place to find cholangial carcinomas (50%). Cancers at this site are called Klatskin tumors.

- Diseases of the biliary tree are typically classified as intrahepatic and extrahepatic.

Biliary tract vocabulary

- "*Chole*…" refers to bile, aka "gall…"
- "*Cholecyst*…" refers to the gallbladder
- "*Choledochal*" refers to the common bile duct

- Gallbladder anatomy
  - There is a high degree of variability in gallbladder anatomy due to variations in embryologic development.



Surgical anatomy of the gallbladder

Organ part	Description	Clinical significance
Fundus	Region beyond the liver edge, site of maximal contraction	Site of elicited pain in Murphy sign
Body	Segment with maximum elasticity	
Neck	Tapering, aka infundibulum	·Hartmann pouch, if present, is useful for grasping during surgery ·Site of obstruction of larger stones

Cystic duct	Tubular connection to CBD[1]	Spiral valves of Heister are site of small stone obstruction
Calot triangle	Borders: cystic duct, common hepatic duct, and liver edge	Site of cystic artery, left hepatic artery and lymph nodes
Liver edge	Non-peritoneal surface of GB	GB can be completely buried in the liver or have a mesentery

1. Common bile duct, 2. Gallbladder

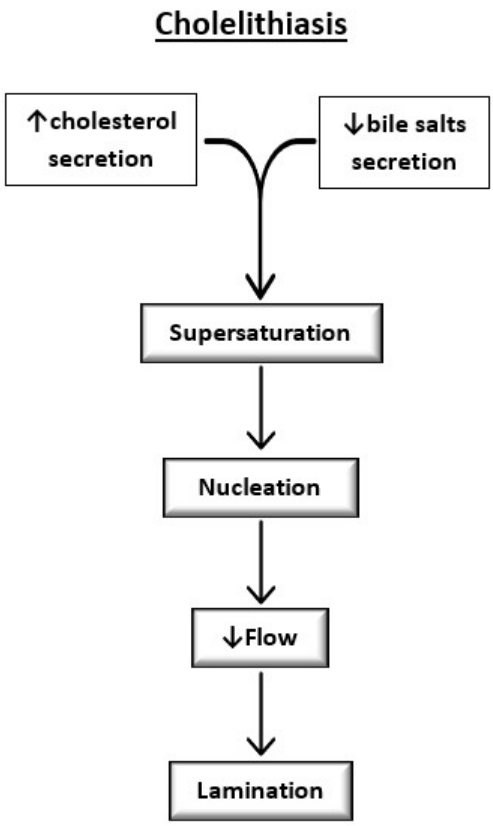
- Histology of the gallbladder
    - The gallbladder lacks a muscularis mucosa. This leads to the mucosal invaginations seen in chronic cholecystitis called the **Rokitansky-Aschoff sinuses**.

Gallbladder histology

Acute cholecystitis

- Pathophysiology
    - Gallstone formation:
        - All stones require the same conditions:
            - Supersaturation
                i. Most stones in the US are cholesterol stones. The cholesterol is held in suspension by **micelles** made of bile salts and phospholipids.
                ii. Saturation can be due to ↑cholesterol (estrogen, familial, ethnic (Pima Indians), obesity (aromatase) or ↓bile salts (Crohn disease).
            - Nidus
                i. Crystals require a structure upon which to form. In the gallbladder, this is usually “sludge”, made of mucus and debris.
            - Decreased fluid flow
                i. Hydration is a key to stone prevention. Decreased bile flow is seen with dehydration and pregnancy due to the smooth muscle relaxation effect of progesterone.
            - Lamellation

i. Stones require repeated episodes of layering (i.e. lamella) to become big enough to obstruct the cystic duct, which has a normal diameter of 1-5 mm.



- Gallstones are common in adults. The stone must be obstructing the cystic duct to explain a patient's symptoms.
  - 16% of adult females and 8% of adult males have gallstones. Most are asymptomatic.

- Only about 20% of people with gallstone will have symptoms over 10-15 years.

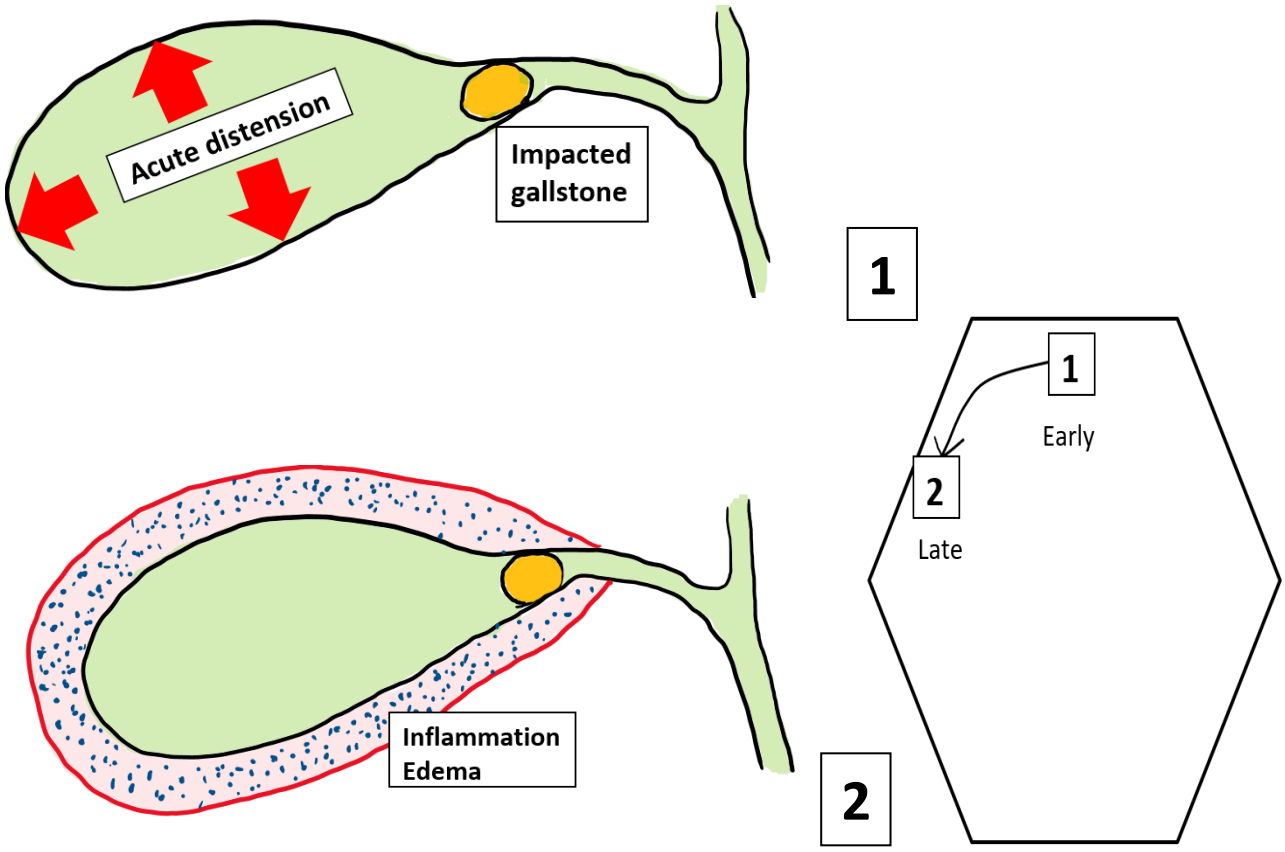
Types of gallstones

- *Cholesterol stones*: more than 90% of gallstones in the US are composed of cholesterol, which has a yellow color. They arise from conditions that cause cholesterol supersaturation in bile. The addition of bilirubinate gives them a green to black coloration.
- *Black pigment stones*: these are formed of bilirubinate are seen in hemolysis.
- *Brown pigment stones*: these are seen with chronic bacterial or parasitic infections

Cholesterol *Pigment* *Brown*

- Obstruction of the cystic duct
  - Pain from distention:
    - the GI tract has sensory innervation only for inflammation and rapid distension. The sensory nerves , called C fibers, are unmyelinated and travel to the CNS via the vagus nerve. These are non-localizing, and the brain makes an estimation of its likely origin. This is ***referred pain***, called ***visceral*** pain by surgeons, and for the gallbladder is placed in the epigastrium.
    - ***Colicky pain*** is seen when there is obstruction of a hollow organ. This is seen in:
      i. Acute cholecystitis
      ii. Stone in the ureter
      iii. Small bowel obstruction
  - Pain from inflammation: as the obstruction continues, there is breakdown of the mucosa and invasion of the gallbladder wall by bacteria. This causes an acute inflammatory response with edematous thickening of the gallbladder wall. When the entire wall is inflamed, the overlying peritoneum is involved. Peritoneum is innervated by lumbar nerves. These are myelinated Aδ fibers and are localizing, called ***somatic pain*** by surgeons. The patient's pain moves

to the RUQ. When the peritoneum of the gallbladder fundus travels over palpating fingertips during inspiration, pain increases, called the **Murphy sign**.

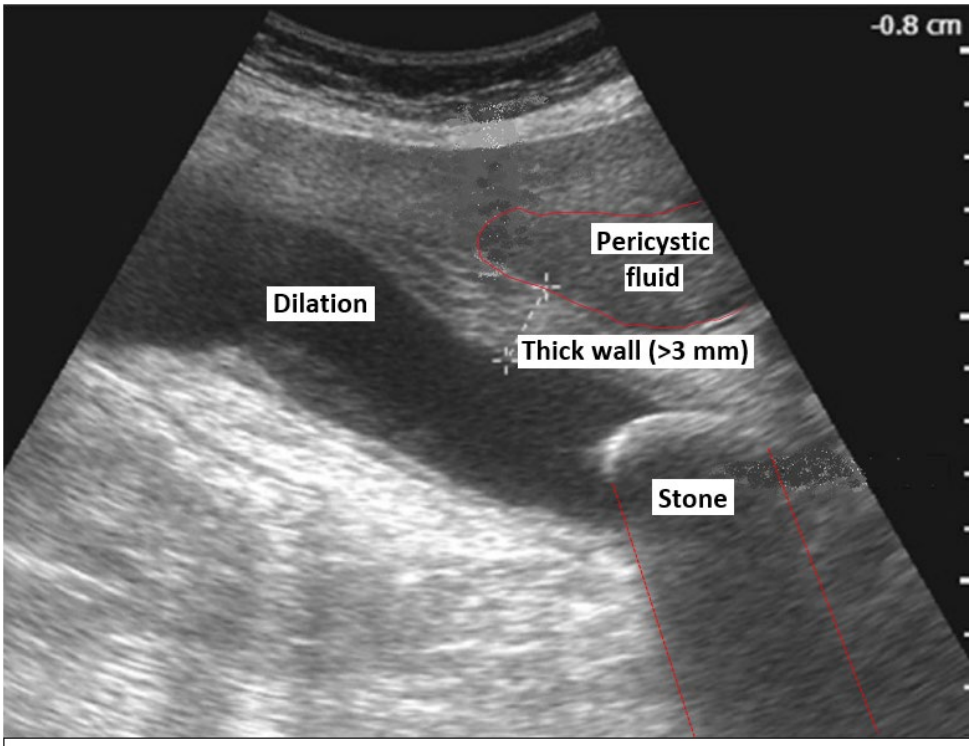


- Presentation:
  - Symptoms: Occur in 2 phases:
    - Early: a colicky epigastric pain
    - Late: over several hours, the pain becomes steady and move to the RUQ.

Acute cholecystitis and the 4 F's

The most common patient to have acute cholecystitis is "fat, female, fertile and forty". While a cheeky mnemonic, it is true. Fat (↑aromatase), female and fertile are all states with increased estrogen, which increases cholesterol synthesis. Pregnancy also has increased progesterone, which relaxes smooth muscle, leading to decreased rates of bile flow. An older age is needed to provide the time for lamellation and formation of a stone large enough to obstruct the cystic duct.

- Signs: no findings during the epigastric phase, (+) Murphy sign when the pain is in the RUQ.
- Diagnosis: obstruction of the gallbladder neck, usually by a gallstone, with thickening of the gallbladder wall due to edema (>3mm), edema in the pericystic space and dilation of the gallbladder.



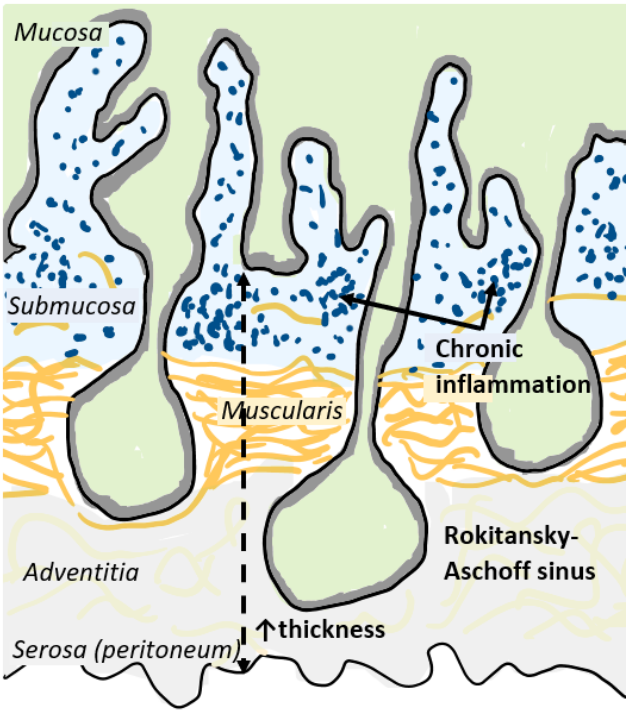
Acute cholecystitis by ultrasound

Image courtesy of Cwik, Grzegorz et al. *Surgical endoscopy* vol. 27,7 (2013): 2561-8. doi:10.1007/s00464-013-2787-9

- Natural history
  - Treatment
    - This varies by country. In the US, acute cholecystitis is treated by cholecystectomy. This is a curative treatment that precludes later perforation and cancer. In Europe, patients may be managed with pain control over several days, after which there is usually remission of symptoms.
  - Complications
    - Perforation of the gallbladder is life-threatening
    - Gangrenous cholecystitis: Full-thickness necrosis of the gallbladder wall leads to perforation and bile peritonitis. Often gas formation can be appreciated in the wall of the gallbladder. This is a life threatening condition.
    - Carcinoma of the gallbladder is a small risk over decades. This is an aggressive malignancy with a poor prognosis.

Chronic cholecystitis

- Pathophysiology:
  - A clinical pathologic entity characterized by recurrent abdominal pain from bouts of acute cholecystitis due to gallstones
  - It can be identified by imaging which shows a contracted gallbladder with a thickened wall from fibrosis or by gallbladder dysfunction. This can be identified by a **HIDA nuclear scan** (see below) with CCK injection. A normal gallbladder ejection fraction should be >35%.
  - Pathology:
    - Chronic inflammation of a gallbladder wall thickened by fibrosis.
    - Rokitansky-Aschoff sinuses: the raised pressure in the gallbladder from contracting against cystic duct obstruction leads to mucosal pouch formation into the submucosa.



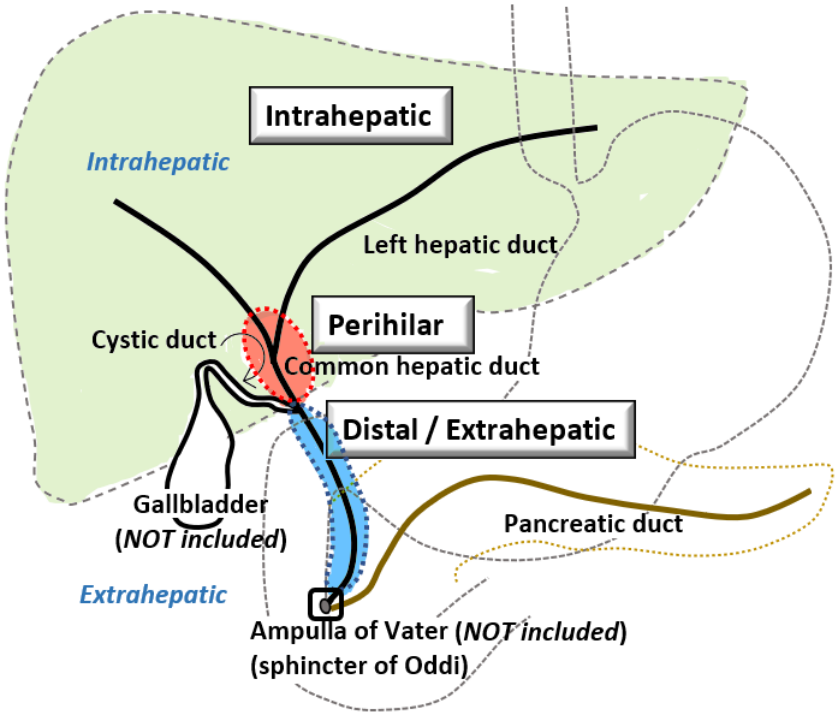
Pathology of chronic cholecystitis

- Presentation:
  - Symptoms:
    - Dyspepsia: a non-specific term used to describe disagreeable sensation that occur with eating, including pain, gas, and nausea.
    - Recurrent epigastric pain: from episodes of acute cholecystitis
  - P/E: usually non-contributory, although a (+) Murphy sign may be found with acute cholecystitis

- Testing:
    - Imaging:
        - Gallstones
        - shrunken gallbladder, thickened wall, usually enhanced as it is due to inflammation and fibrosis.
        - Calcification of the wall: this may be seen on an abdominal X-ray
    - **HIDA scan with CCK**: the tracer is excreted by the liver at a fast enough rate that it outlines the biliary tree. If the gallbladder is not visualized, then it is occluded (i.e. acute cholecystitis). If the gallbladder is seen, the CCK can be injected, and the contraction of the gallbladder quantitated. An ejection fraction <35% is the sign of a dysfunctional gallbladder.
- Natural history:
    - Prognosis
    - Complications (30% lifetime risk):
        - Ascending cholangitis: with a common bile duct stone
        - Gallstone pancreatitis: with common bile duct stone in the Ampulla
        - Cancer: a 5-10% risk over decades
    - Treatment: cholecystectomy is curative.

Cholangiocarcinoma

- Classification:
    - Traditional classifications designated intrahepatic cholangiocarcinomas as primary liver cancers. Extrahepatic cholangiocarcinomas were classified as gallbladder, extrahepatic ducts, and ampulla of Vater. Current classification is now:
        - Intrahepatic(10%)
        - Perihilar (50%)
        - Distal (or extrahepatic) (40%)
            - This does not include the gallbladder or ampulla of Vater.



Cholangiocarcinomas: anatomic classification

- Pathophysiology:
  - Risk factors:
    - Primary sclerosing cholangitis
      - Accounts for 30% of cholangial carcinomas
      - Associated with smoking and drinking
    - Hereditary conditions:
      - Lynch syndrome
      - BRCA
      - Cystic fibrosis
      - Liver flukes, e.g. *C. sinensis*
  - Pathology: adenocarcinomas arising from dysplasia of the bile duct epithelium. There is no clear molecular pathogenesis
- Presentation:
  - Symptoms:
    - Biliary obstruction: jaundice, pale stools, brown foamy urine
    - RUQ pain and weight loss
  - P/E:
    - Biliary obstruction: jaundice, Courvoisier gallbladder
    - Mass in the RUQ

    - Testing:
        - Laboratory: cholestatic pattern: ↑Alk phos / GGT
        - Imaging: mass and duct obstruction; confirmation by biopsy
- Natural history:
    - Prognosis: typically present late with advanced local disease and survival in months
    - Complications: most of the worst symptoms are caused by biliary obstruction
    - Treatment is palliative with stenting for biliary duct obstruction

Gallbladder carcinoma

- Pathophysiology:
    - Risk factors: the most significant is cholelithiasis
    - Progression: like other GI adenocarcinomas, this follows the progression of dysplasia to carcinoma over years to decades
    - Molecular pathways: these are not well established, although KRAS mutations are common in the dysplasia/neoplasia malignancies (compared to the β-catenin mutations of the adenoma/carcinoma sequences).
- Presentation:
    - Symptoms: most commonly are incidental findings at time of symptomatic gallbladder disease. If symptomatic due to the cancer, pain is the commonest symptom.
    - P/E: usually non-contributory. A palpable mass is possible.
    - Testing: imaging with biopsy confirmation
- Natural history:
    - Prognosis: while this depends on stage, >90% of symptomatic patients present with advanced disease. For these, 5 year survival is <10%.
    - Complications: biliary obstruction
    - Treatment: surgical resection of local disease can be curative (65% 5 year survival).

Ampullary carcinoma

- Pathophysiology:
    - The ampulla of Vater is formed by the duodenal aspect of the sphincter of Oddi muscle, which surrounds the confluence of the distal CBD and main pancreatic duct. Ampullary carcinomas are defined as those that arise within the ampullary complex, distal to the bifurcation of the distal CBD and the pancreatic duct.
    - Behavior is that of intestinal epithelium, not pancreaticobiliary epithelium. This means that carcinoma typically progresses through the adenoma/carcinoma sequence (and not the dysplasia/carcinoma sequence).
    - Molecular pathways are similar to those of other intestinal neoplasms with mismatch repair deficiencies the commonest defect.
        - Ampullary carcinomas are increased in the hereditary neoplasias of the intestine: Lynch syndrome and familial adenomatous polyposis syndrome.

- Presentation:
  - Symptoms: 80% present with obstructive jaundice
  - P/E: usually non0contributory
  - Testing:
    - Laboratory tests: cholestatic pattern (↑Alk phos /GGT)
    - Imaging: US will show the dilated common bile duct but usually not the tumor, as it is too small
    - ERCP (endoscopic retrograde cholangiopancreatogram) is the best procedure as it allows for visualization of the mass, biopsy, and injection of the biliary tree.
- Natural history:
  - Prognosis: depends on the stage. There is a 75% 5 year survival with complete resection and negative lymph nodes. If lymph nodes are positive, 5 year survival is <50%.
  - Complications: biliary obstruction
  - Treatment: only surgery is curative