GALL BLADDER CANCER

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BACKGROUND

- Cancers of the biliary tract include cholangiocarcinoma (cancers arising from the bile duct epithelium), ampulla of Vater cancer, and gallbladder cancer
- All subtypes of biliary tract cancers are rare and have an overall poor prognosis
- Difficult to diagnose
- Gallbladder cancer is the 5th most common GI cancer and the most common hepatobiliary cancer in US
- Gallbladder cancer accounts for 46% of the biliary tract cancers in US

PATHOPHYSIOLOGY
CAUSES OF GALL BLADDER CANCER

- Chronic inflammation
  - Gall stones
    - >75%, cholesterol gall stones
    - The presence of gallstones increases the risk of gallbladder cancer 4- to 5-fold
  - Primary sclerosing cholangitis, ulcerative colitis, liver flukes, chronic *Salmonella typhi* and paratyphi infections, and *Helicobacter* infection
- Ingestion of certain medications (eg, oral contraceptives, INH, methyldopa) can increase the risk of gallbladder cancer
- Certain chemical exposures (eg, pesticides, rubber, vinyl chloride氯乙烯)

PATHOPHYSIOLOGY
CAUSES OF GALL BLADDER CANCER

- Occupational exposures
  - Textile, petroleum, paper mill, and shoemaking
- Exposures through water pollution (organopesticides, eg, dichlorodiphenyltrichloroethane-DDT and benzene hexachloride林丹); heavy metals (eg, cadmium鎘, chromium鉻, lead); and radiation exposure (eg, radon氡 in miners)
- Obesity
  - Association with gallstones, increased endogenous estrogens, or through the ability of fat cells to secrete a large number of inflammatory mediators

PATHOPHYSIOLOGY

CAUSES OF GALL BLADDER CANCER

- Hereditary syndromes
  - Gardner syndrome, neurofibromatosis type I, and hereditary nonpolyposis colon cancer
- Oncogenic mutations
  - polymorphism of the cytochrome P450 1A1 gene (*CYP1A1*), encodes a protein involved in catalyzing the synthesis of cholesterol and other lipids
  - Polymorphisms within the apolipoprotein B gene
- Overexpression of alpha-methylacyl coenzyme A racemase (AMACR)
- Abnormal anatomy
  - Congenital defects with anomalous pancreaticobiliary duct junctions
  - Choledochal cysts

PATHOPHYSIOLOGY
RELATIVE RISK

Risk factor	Relative risk		Reference
Gallstones	3.01-23.8		218-222
Size of gallstones			
2.0-2.9 cm	2.4		191,223
>3.0 cm	9.2-10.1		
Duration of gallstones			
5-19 yr	4.9		193
>20 yr	6.2		
BMI	Men	Women	215
30.0-34.9	1.8	2.1	
Infections			
Chronic typhoid & paratyphoid carriers	12.7-167		224,225
Helicobacter bilis	2.6-6.5		206,226

FREQUENCY
UNITED STATES

- 10,000 new cases of gallbladder cancer and other biliary cancers are predicted in 2013 according to the American Cancer Society 2013 statistic projections
- Gallbladder cancer is more common in women
- The incidence of gallbladder cancer rises with age
  - 75% with gallbladder cancer > 64 years

FREQUENCY
WORLD WIDE

- Incidence of gallbladder cancer worldwide (From National Cancer Institute. Surveillance, Epidemiology and End Results (SEER) Program)

FREQUENCY
WORLD WIDE

- Incidence varies substantially with racial and ethnic group and sex
  - Gallbladder cancer rates are the highest among American Indians/Alaska Natives and among white Hispanic (西班牙血統) peoples
- Areas with the highest incidence rates
  - India, Korea, Japan, Czech Republic捷克, Slovakia斯洛伐克, Spain, Columbia, Chile, Peru, Bolivia玻利維亞, and Ecuador厄瓜多爾
- The United Kingdom, Denmark, and Norway have the lowest international incidence rates (<2/100,000)

CLINICAL PRESENTATION

HISTORY

- Overlap with the symptoms of gallstones and biliary colic
- Abdominal pain may be of a more diffuse and persistent nature than the classic right upper quadrant pain of gallstone disease
- Jaundice, anorexia, and weight loss often indicate more advanced disease

CLINICAL PRESENTATION

SIGNS AND SYMPTOMS

- Usually not present until the later stages of gallbladder cancer
- Jaundice
- Pain above the stomach
- Fever
- Nausea and vomiting
- Bloating
- Lumps in the abdomen
- Jaundice, anorexia, and weight loss often indicate more advanced disease

CLINICAL PRESENTATION
SIGNS AND SYMPTOMS

- Palpable mass in the right upper quadrant (Courvoisier sign, if this is due to a palpable gallbladder)
- Periumbilical lymphadenopathy (Sister Mary Joseph nodes)
- Left supraclavicular adenopathy (Virchow node)
- Pelvic seeding: Mass is palpated on digital rectal examination (Blumer shelf)

DIFFERENTIAL DIAGNOSES

- Biliary Colic
- Acalculous cholecystitis
- Acalculous cholecystopathy
- Ampullary carcinoma
- Bile duct stricture
- Bile duct tumors
- Biliary disease
- Biliary obstruction
- Carcinoma of ampulla Vater
- Cholangiocarcinoma
- Cholangitis
- Cholecystitis
- Choledochal cysts
- Cholecholithiasis
- Cholelithiasis
- Clostriadial cholecystitis
- Gall bladder mucocele
- Gall bladder volvulus
- Hepatic carcinoma, primary
- Liver abscess
- Pancreatic cancer
- Primary biliary cirrhosis
- Primary sclerosing cholangitis

WORKUP
LABORATORY STUDIES

- Tumor marker CA 19-9
  - CA 19-9 may be significantly elevated in both cholangiocarcinoma and gallbladder cancer
  - CA 19-9 tests may be helpful in the appropriate situation if the clinical suspicion for gallbladder cancer is high
- Liver function tests: Elevated alkaline phosphatase and bilirubin levels are often found with more advanced disease
- CBC: Anemia may be an indicator of more advanced disease

WORKUP
IMAGE STUDIES

- Ultrasonography (US)
  - Standard initial study in patients with right upper quadrant pain
  - A mass can be identified in 50-75% of patients with gallbladder cancer
  - Also can delineate metastatic lesions in the liver
- Computed tomography (CT) scans
  - Can demonstrate tumor invasion outside of the gallbladder and identify metastatic disease elsewhere in the abdomen or pelvis
  - Liver invasion occurs in 60% of cases, and the combination of CT scan and US provides accurate details of disease extension

WORKUP
IMAGE STUDIES

- Magnetic resonance imaging (MRI)
  - Useful in examining this region for disease extension into other tissues or metastatic disease in the liver
  - Provide details of the vasculature for preoperative planning via magnetic resonance angiogram (MRA) and bile duct passages via magnetic resonance cholangiogram (MRCP)

WORKUP
IMAGE STUDIES

- Cholangiography
  - Via a percutaneous route, or endoscopic retrograde cholangiography (ERCP)
  - May establish the diagnosis of gallbladder cancer by bile cytology
- Endoscopic ultrasonography
  - Useful to assess regional lymphadenopathy and depth of tumor invasion into the wall of the gallbladder
- Angiography
  - May be used to confirm encasement of the portal vein or hepatic artery and may assist in preoperative planning for definitive resection

TNM STAGING (AJCC, 7TH ED)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1a	Tumor invades lamina propria
T1b	Tumor invades muscular layer
T2	Tumor invades perimuscular connective tissue
T3	Tumor perforates serosa or directly invades the liver and/or one other adjacent organ
T4	Tumor invades main portal vein or hepatic artery or invades multiple extrahepatic organs
NX	Regional nodes cannot be assessed
N0	No regional nodal metastasis
N1	Metastasis to nodes along the cystic duct, common bile duct, hepatic artery and/or portal vein
N2	Metastasis to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes*
M0	No distant metastasis
M1	Distant metastasis

Stage 0		Tis	N0	M0
Stage I		T1	N0	M0
Stage II		T2	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

* Denotes changes from 6th edition classification.

PROGNOSIS

SURVIVAL RATE

Stage	5-Year Survival Rate
0	80%
I	50%
II	28%
IIIA	8%
IIIB	7%
IVA	4%
IVB	2%

TREATMENT
SURGERY

- Curative surgery
  - Cholecystectomy
  - Extended cholecystectomy with lymphadenectomy
- Palliative surgery
  - Biliary bypass
  - Endoscopic stent placement
  - Percutaneous transhepatic biliary drainage

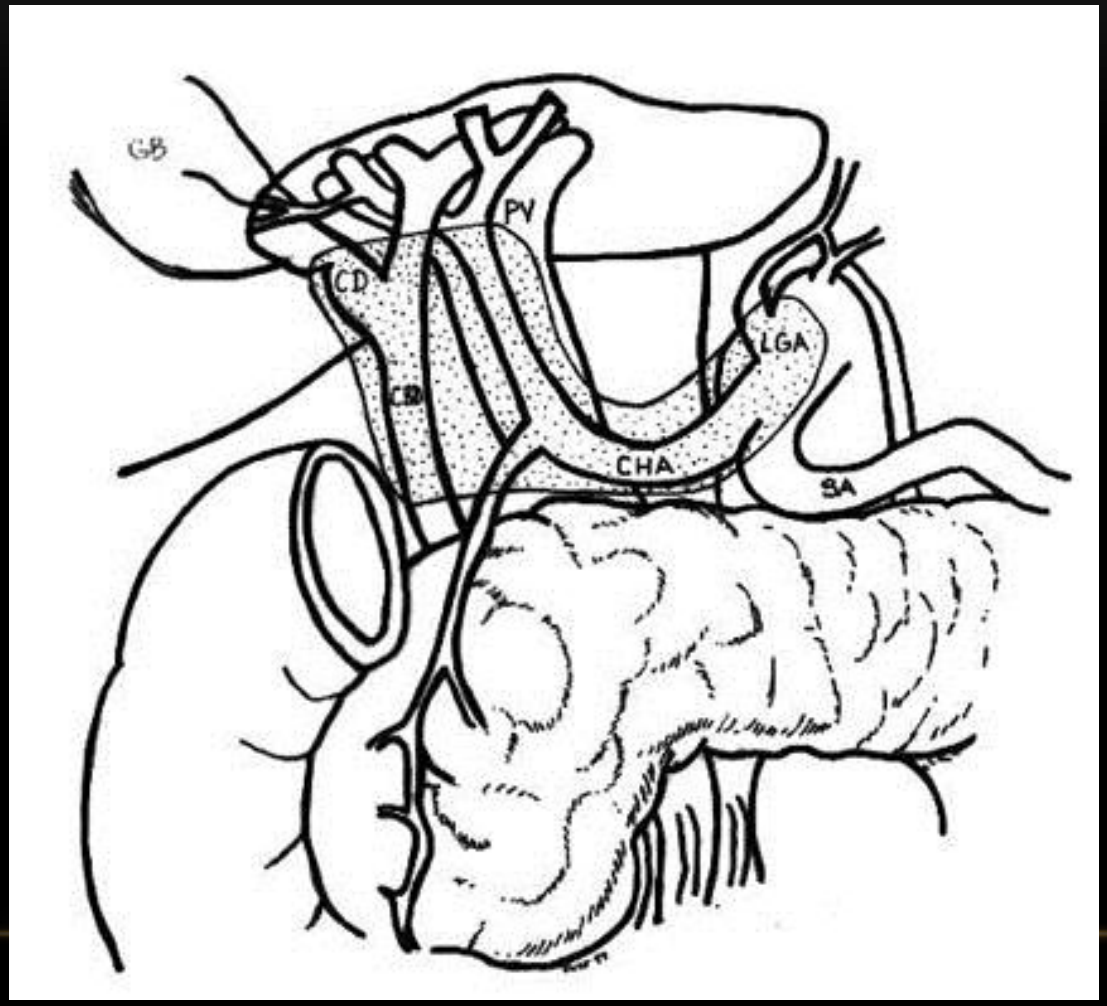
TREATMENT
ADJUVANT THERAPY

- Radiotherapy
  - External beam
  - Internal beam (brachytherapy)
- Chemotherapy
  - Gemcitabine, Capecitabine, Oxaliplatin, 5-Flurouracil and Cisplatin

TREATMENT
ACCORDING TO STAGES

Stage	Treatment
1	Cholecystectomy alone
2	Extended cholecystectomy CCRT
3	Extended cholecystectomy R/T, CCRT
4	Palliative therapy with R/T, C/T Stents

THE EXTENT OF LYMPHADENECTOMY FOR GALLBLADDER CANCER



Thank you