Cancer of the liver and pancreas

- Describe hepatocellular and cholangiocarcinoma.
- Understand the frequency of metastatic disease to the liver.
- Recognize the rarity of primary liver neoplasms in children.
- Recognize all aspects of pancreatic carcinoma.

Black: original content
Red: Important
Green: only found in males slides

Orange: Doctor notes
Grey: Extra/Robbins
Purple: Only found in females slides

Reviewed by: Razan AlRabah & Ibrahim AlDakhil

Editing File

Hepatocellular Carcinomas

Introduction

- Metastatic tumors are more common in liver then primary carcinomas.
  - Primary carcinomas commonly arise from:
    - Hepatocytes → hepatocellular carcinoma.
    - Bile duct → Cholangiocarcinomas.
    - Other rare forms: hepatoblastomas and angiosarcomas.

Epidemiology

- **Male** predominance.
- **Chronic HBV infection:**
  - > 85% of the cases, vertical transmission from mother to infant (carrier stage), increase risk of HCC 200 folds.
- **Cirrhosis:**
  - 85% to 90% of cases of HCC. In the Western[1] world where HBV is not prevalent, in the setting of other chronic liver diseases.

Pathogenesis (hepatocarcinogenesis)

Chronic Viral infection	Cirrhosis	Chronic Alcoholism
• Most common worldwide • HBV • HCV[2]	Important but not requisite	Most common In the US

Food contaminants	Metabolic syndrome	Other conditions
High exposure to **aflatoxins**: - Highly carcinogenic toxins. - From: Aspergillus flavus - Found in: moldy grains and peanuts[3].	• Obesity • Diabetes mellitus • Nonalcoholic fatty liver disease (NAFLD)	• Tyrosinemia[4] • Hereditary hemochromatosis[5]

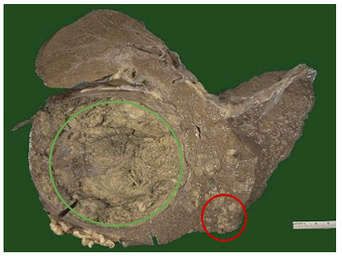
Aflatoxins combined with HBV infection increases the risk for HCC dramatically.

1- Due to alcoholism.
2- More severe if co-infection with HBV.
3-If a hepatitis patient eats it, the risk increases.
4- Hereditary tyrosinemia type I is an autosomal recessive error of tyrosine catabolism caused by a deficiency of the enzyme fumarylacetoacetase an enzyme expressed primarily in the liver and kidneys this lead to accumulation of Fumarylacetoacetate a pathogenic and mutagenic metabolite that reduces intracellular levels of glutathione.
5- Hemochromatosis is caused by mutation in HME gene that lowers hepcidin levels or diminish its functions causing excessive absorption of iron.

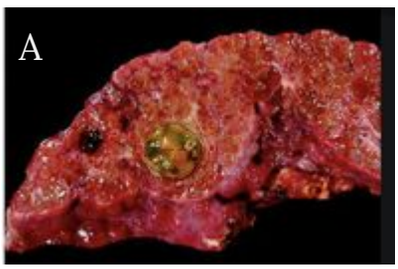
Hepatocellular Carcinomas

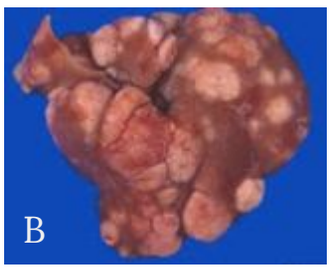
Morphology

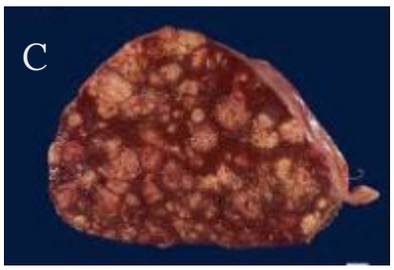
Gross



- Large and bulky.
- Greenish cast contains bile.
- Small satellite nodules.
- Appears: (A) **Unifocal**, (B) **multifocal** or (C) **diffusely infiltrative**.
  - Theses patterns may cause: liver enlargement or invasion of vascular channels.

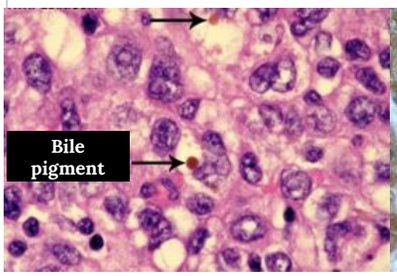


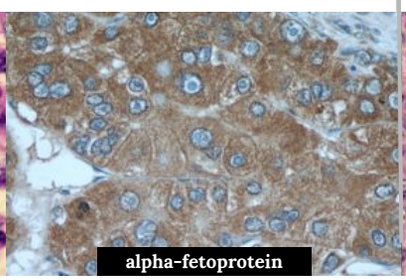


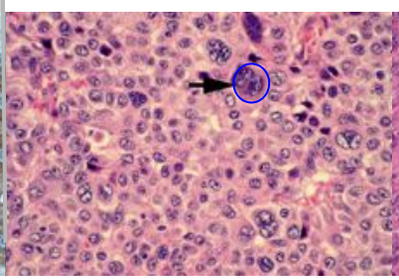


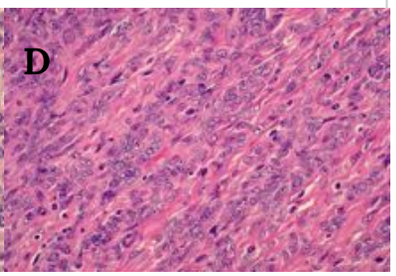
Microscopic

well-differentiated & moderately differentiated	Poorly differentiated
• Cells recognizable as hepatocytic in origin. • Presence of **bile pigment.** • May be +ve for **alpha-fetoprotein**[1]**.**	• Pleomorphic. • Numerous anaplastic giant cells. • Small & completely undifferentiated. • **Thickening** of the liver cell plates 4-6 cells, (normally they are 1-2 cells thick). (D&E)



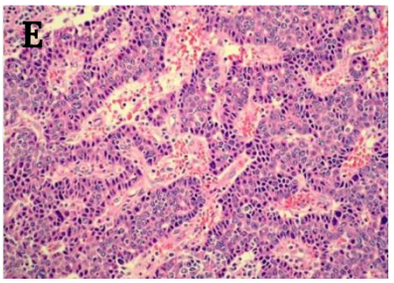


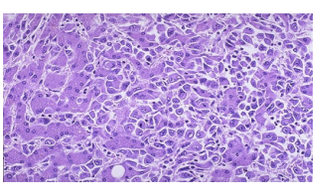




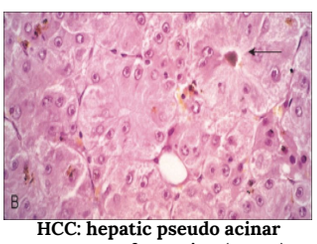
Metastases

- Extensive **intrahepatic** metastases.
- Invasion of the **portal vein** and circulation → inferior vena cava → right side of the heart.
- **Lymph node:**
  - Perihilar.
  - Peripancreatic.
  - Para aortic above and below diaphragm.





Righ: well differentiated malignant HCC cells.
Left: normal hepatocytes.



HCC: hepatic pseudo acinar structures formation (arrow)

1- Naturally synthesized in embryo's liver, but abnormal to find in adult.

Hepatocellular Carcinomas

Clinical features

Ill-defined upper abdominal pain

Malaise

Fatigue

Feeling of abdominal fullness

Weight loss

- Palpable enlarged liver.
- Uncommon: Fever and jaundice.

Laboratory findings

- Elevated levels of serum **α-fetoprotein** in 50% to 75% of patients with HCC.

Death usually occurs from

1 Cachexia

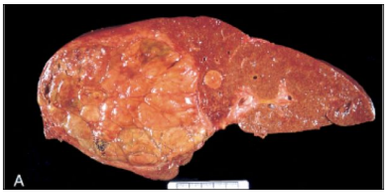
2 Gastrointestinal bleeding or esophageal variceal bleeding.

3 Liver failure with hepatic coma[1].

4 Rupture of the tumor with fatal hemorrhage.

Fibrolamellar Carcinoma

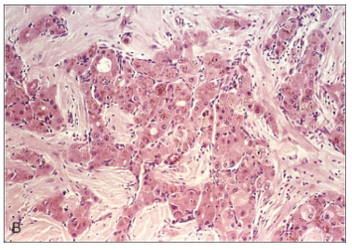
- A distinctive variant of hepatocellular carcinoma.
- In **young** male & female adults (**20-40** years).
- No association with HBV or cirrhosis.
- Better prognosis.



Morphology

Gross:

- Single and large.
- Hard “scirrhous”.
- **Fibrous bands** coursing through.



Microscopic:

- Well-differentiated polygonal cells in nests or cords.
- Separated by parallel lamellae of **dense collagen bundles.**

Cholangiocarcinoma

Introduction

- It is a malignancy of the biliary tree, arising from bile ducts within and outside of the liver.
- Second most common primary malignant tumor of the liver.
- Occurs in non cirrhotic livers.

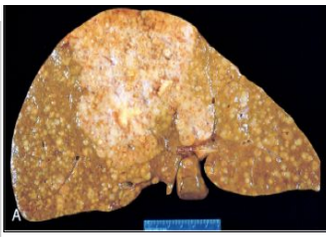
Risk factors

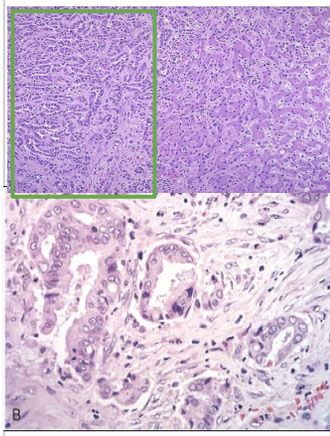
- Primary sclerosing cholangitis.
- Congenital fibropolycystic diseases of the biliary system:
  - Caroli disease
  - Choledochal cysts
- Previous exposure to Thorotrast (formerly used in the radiography of the biliary tract).
- In the orient due to chronic infection of the biliary tract by the liver fluke[1] Opisthorchis sinensis (Parasitic trematodes).

Morphology

Macroscopic	• Intrahepatic cholangiocarcinoma occurs in non-cirrhosis • A treelike tumours mass within the liver or a massive tumor nodule. • Lymphatic and vascular invasion are common.

Microscopic	• Resemble adenocarcinoma, microscopically it is nearly impossible to differentiate it from adenocarcinoma (well-moderately differentiated)
	• Growing as glandular/tubular structures:
	  ○ Lined by malignant epithelial cells.
	  ○ Surrounded by **desmoplasia** of the stroma.
	• **Mucin producing** adenocarcinomas.
	• **Rarely bile stained**, because differentiated bile duct epithelium does not synthesize bile.
	• Mixed variants occur, in which elements of both HCC and cholangiocarcinoma are present.





Clinical features

Detected late in its course, as a result of obstruction to bile flow or a symptomatic liver mass.

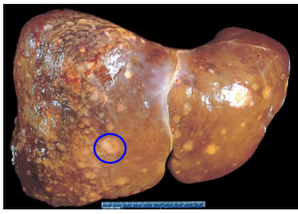
Hematogenous Metastases: Lung, bones (mainly vertebrae), adrenals, brain. Or Regional **lymph node.**

Aggressive surgery is the only choice for long-term survival due to poor prognosis.

Alpha-fetoprotein Is not elevated.

Metastatic tumors

- More common than primary neoplasia.
- Any cancer in any site may spread to the liver (including leukemias and lymphomas), but the most common types are: breast, lung and colon.



Morphology

- Multiple nodular metastases that may replace 80% of hepatic parenchyma causing hepatomegaly (The liver weight increases).
- Mass lesions variable in size, larger ones demonstrate central necrosis.

Angiosarcoma

- Cirrhosis is present in 20% to 40% of cases.
- **Risk factor:** vinyl chloride[1] and thorotrast[2] exposure(working in factories).

Morphology

- Pleomorphic endothelial cells with large hyperchromatic nuclei.
- Giant cells in frequent mitosis and irregular anastomosing vascular channels.
- Spindle shaped cells.

Hepatocellular Adenoma

- **Benign neoplasms** developing from hepatocytes.

Risk Factors	Clinical Features	Microscopy

Sex hormone exposure (ex: oral contraceptives, anabolic steroids)	• Detected as: hepatic mass on abdominal imaging or when they cause symptoms.
	• **Symptoms:**
	  ○ Pain
	  ○ Rupture causing life threatening intra abdominal bleeding.
		Normal hepatocytes and absence of portal tracts.

1- Substance used in plastic factories.
2- Radiocontrast agent (no longer used).

Pancreatic Carcinoma

Introduction

- It is adenocarcinoma of the exocrine pancreas arises from ductal epithelial cells.
  - 60% arise in the head of the gland.
  - 15% in the body.
  - 5% in the tail.
  - 20% diffusely involves the entire gland.
- Diagnosed at an advanced stage, accounting for the high mortality rate[2].

Epidemiology

- It occurs in the 6th to 8th decade.
- Blacks > whites.
- Males > females.
- Diabetics > non diabetics.

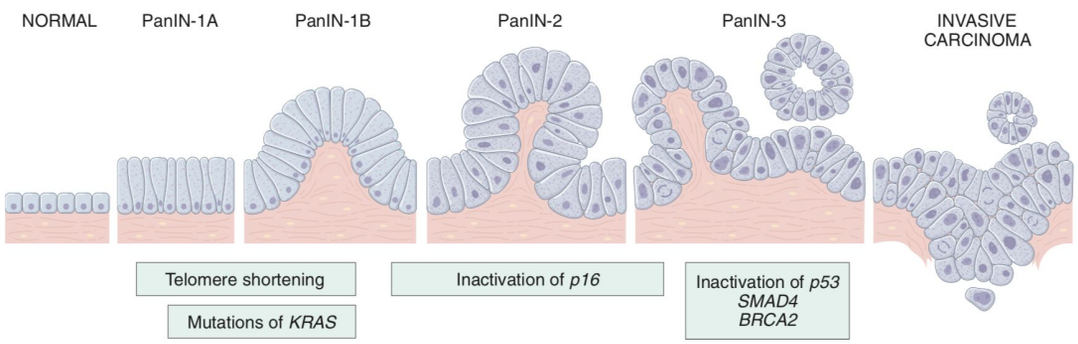
Risk Factors

- **Smoking** doubles the risk.
- Long standing chronic pancreatitis and diabetes mellitus.
- Germ line mutations of the familial breast/ovarian cancer gene **BRCA2** seen in 10% of cases arising in individuals of Ashkenazi origin[1],

Pathogenesis

- Pancreatic cancer arises as a consequence of inherited and acquired mutations in cancer associated genes.
- Four genes are most commonly affected by somatic mutations:

KRAS, CDKN2A/p16, SMAD4, and TP53



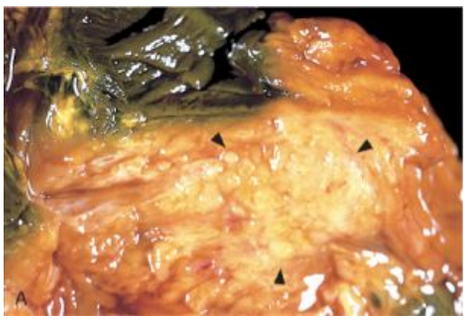
Robbins:
Progression model for the development of pancreatic cancer. It is postulated that telomere shortening and mutations of the KRAS oncogene occur at early stages, inactivation of the p16 tumor suppressor gene occurs at intermediate stages, and inactivation of the TP53, SMAD4, and BRCA2 tumor suppressor genes occurs at late stages. Note that while there is a general temporal sequence of changes, the accumulation of multiple mutations is more important than their occurrence in a specific order. PanIN, Pancreatic intraepithelial neoplasm. The numbers following the labels on the top refer to stages in the development of PanINs.

1- Because of familial marriage.
2- Tumor marker CK19.9

Pancreatic Carcinoma

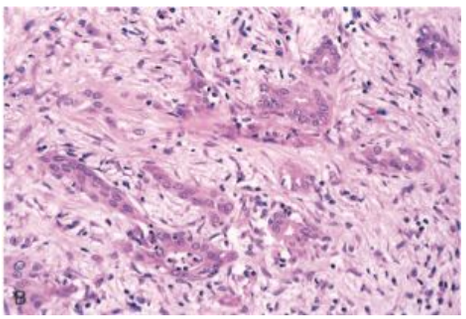
Morphology

Macroscopic



- Majority are ductal carcinoma.
- Hard.
- Stallete.
- Gray-white.
- Poorly defined masses.

Microscopic



- Highly invasive.
- Elicits an intense non-neoplastic host reaction called a "desmoplastic response".

Metastasis

Lymph nodes	Distant
1. Peripancreatic. 2. Gastric. 3. Mesenteric. 4. Omental. 5. Portahepatic.	1. Lungs. 2. Bones.

Less common variants of pancreatic cancer include:

- Acinar cell carcinomas.
- Adenosquamous carcinomas.
- Undifferentiated carcinomas with osteoclast-like giant cells.

Clinical Features

- Jaundice.
- Weight loss.
- Pain.
- Massive metastasis to the liver.
- Migratory thrombophlebitis.

Summary

	Incidence	Etiology	Morphology	Prognosis
Hepatocellular Carcinomas	- Male. - More than 85% of cases of HCC → chronic HBV infection. - Western: cirrhosis 85-90% + chronic liver diseases	1. HBV & HCV. 2. Cirrhosis. 3. Chronic alcoholism. 4. Aflatoxins from aspergillus. 5. Tyrosinemia & hemochromatosis	**Micro:** In well-differentiated tumors, cells that are recognizable as hepatocytic in origin. **+ve alpha-fetoprotein** **Macro:** Satellite nodules & greenish cast	Death occurs from: 1. Cachexia. 2. Variceal bleeding. 3. Liver failure with hepatic coma. 4. Rupture of the tumor with hemorrhage
Fibrolamellar carcinoma	- A distinctive variant of hepatocellular carcinoma. - Young male and female adults (20 to 40 years of age).	No association with HBV or cirrhosis	well-differentiated polygonal cells growing in nests or cords and separated by parallel lamellae of dense collagen bundles	Better prognosis
Hepatocellular Adenoma	Benign neoplasms developing from hepatocytes.	Sex hormone exposure (Oral contraceptive drugs)	Normal hepatocytes and absence of portal tracts.	Rupture cause life threatening intra abdominal bleeding.
Cholangiocarcinoma	Malignancy of the biliary tree, arising from bile ducts.	- Primary sclerosing cholangitis. - Congenital fibropolycystic - Exposure to Thorotrast. - In the Orient : Clonorchis sinensis	**Macro:** - Cholangiocarcinoma Resemble adenocarcinomas. - treelike tumours mass **Micro:** - Well to moderately differentiated. - Rarely bile stained.	- Late detection: as obstruction to bile flow or as a symptomatic liver mass. - Prognosis is poor. - Alpha-fetoprorein is not elevated.
Angiosarcoma	Malignant tumor of endothelial cells.	- Cirrhosis 20-40% - Exposure to vinyl chloride and thorotrast.	- Pleomorphic endothelial cells with large hyperchromatic nuclei. - Giant cells in mitosis. - Spindle shaped cells.	
pancreatic carcinoma	- Ductal epithelial cells. - Most common: Ductal adenocarcinoma. -Less common: 1. Acinar cell carcinomas. 2. Adenosquamous carcinomas. 3. Undifferentiated carcinomas.	- 6th to 8th decade. - Blacks. - Males. - Diabetics. - Cigarette smoking. - K-RAS mutation.	60% arise in the head of the gland - Highly invasive. - Desmoplastic response	One of the highest mortality rates of any cancer. - Jaundice, weight loss, pain, massive metastasis to liver and migratory thrombophlebitis.

Source: 434 team.

Quiz

Q1: Which of the following carcinomas is positive for alpha-fetoprotein?

A) Cholangiocarcinoma
B) Hepatocellular carcinoma
C) Pancreatic carcinoma
D) Angiosarcoma

Q2: Which of the following risk factors is associated with Hepatocellular Adenoma?

A) Thorotrast exposure
B) BRCA2 gene mutation
C) Sex hormone exposure
D) Diabetes

Q3: One of the most common sites of metastatic tumor:

A) Colon
B) Brain
C) Pancreas
D) Bone

Q4: Fibrous Bands and dense collagenous bundles is present in:

A) Cholangiocarcinoma
B) Pancreatic carcinoma
C) Esophageal carcinoma
D) Fibrolamellar carcinoma

Q5: Which of the following is <u>not</u> from the morphology of angiosarcomas?

A) Pleomorphic endothelial cells
B) Dense collagen bundles
C) Spindle shaped cells
D) Giant cells

Q6: Which of the following carcinomas has a scirrhous gross morphology?

A) Intrahepatic cholangiocarcinoma
B) Pancreatic carcinoma
C) Hepatoblastoma
D) Fibrolamellar carcinoma

Q7: What is a characteristic feature of pancreatic carcinomas?

A) Elevated levels of alpha-fetoprotein
B) Desmoplastic response
C) Tree-like tumor mass
D) Dense collagen bundles

Q8: What carcinoma has the highest mortality rate?

A) Fibrolamellar carcinoma
B) Cholangiocarcinoma
C) Pancreatic carcinoma
D) Esophageal carcinoma

Q9: Which of the following genes is <u>not</u> from the four commonly mutated genes in pancreatic carcinomas?

A) P21
B) TP53
C) SMAD4
D) KRAS

1: B 2: C 3: A 4: D 5: B 6: D 7: B 8: C 9: A

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THANK YOU