جامعة الملك سعود
King Saud University

12

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GNT pathology cases file
Don't forget to check it frequently Click

Pathology

Liver and Pancreas Neoplasm

439

Color index
- Important
- Doctor's note
- Extra info
- Main text
- ★ Male's slide
- ★ Female's slide

اللهم لا سهل الا ماجعلته سهلا و انت تجعل الحزن إذا شئت سهلا

Revised & Approved
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Objective

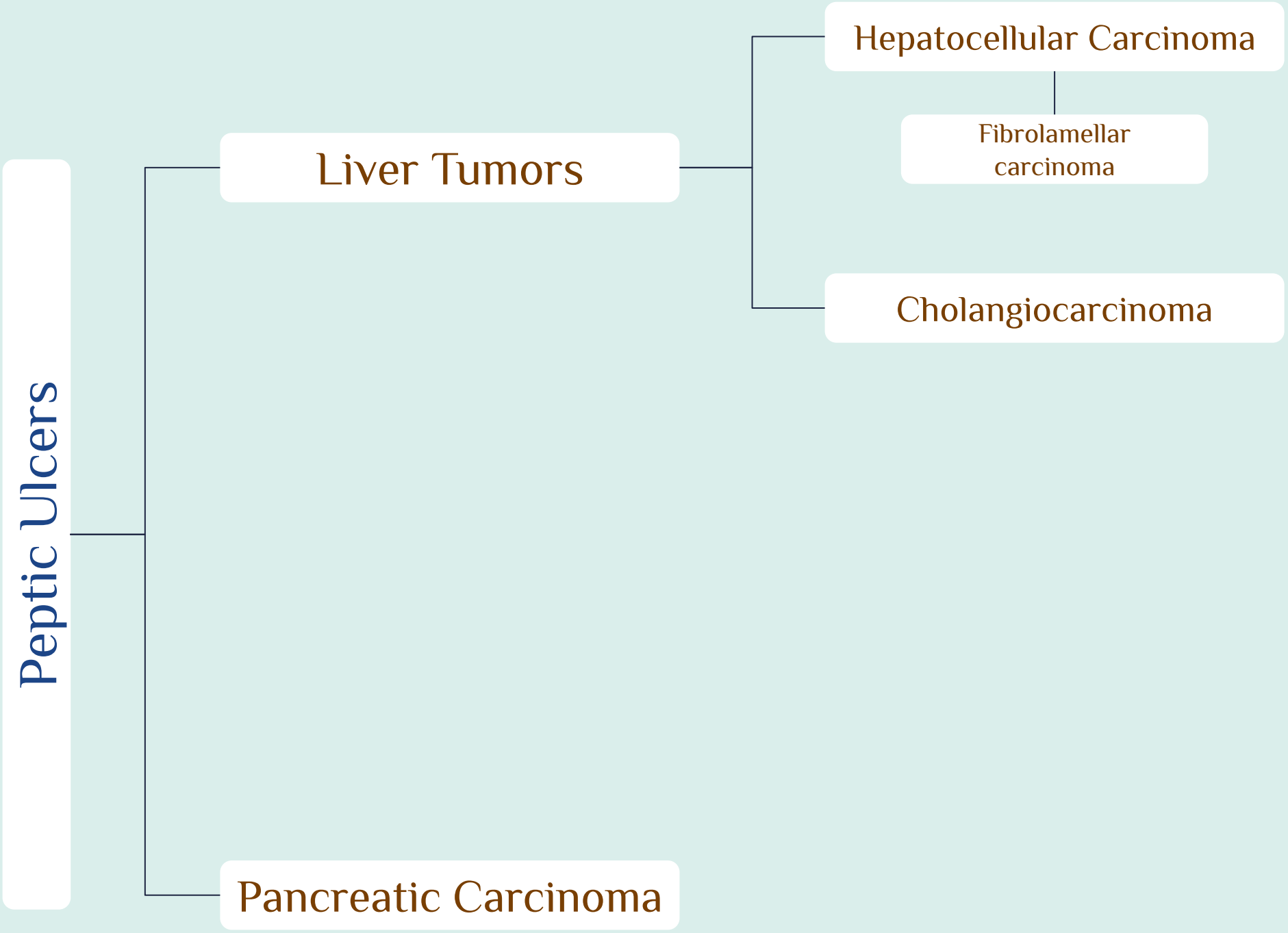
01 Describe most common liver malignancies: Hepatocellular and cholangiocarcinoma

02 Understand the frequency of metastatic disease to the liver

03 Recognize the rarity of primary liver neoplasms in children

04 Recognize all aspects of pancreatic carcinoma

Overview



Liver Tumors

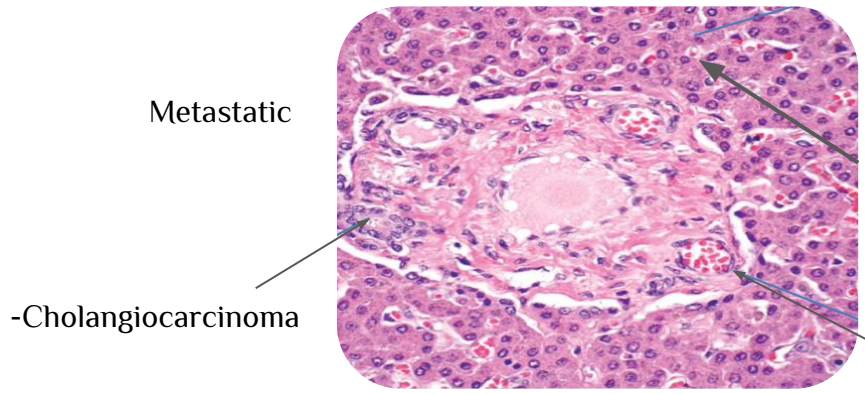
Introduction

Malignant

- **Metastatic**
  Most common liver tumor
- **Primary**
  - Hepatocellular carcinoma
  - Cholangiocarcinoma
  - Hepatoblastoma “rare”
  - Angiosarcoma “rare”

Benign

- Cavernous Hemangioma
- Hepatocellular Adenomas



• **Malignant tumors** occurring in the liver can be **primary** or **metastatic**
• The **liver** and **lungs** are the visceral organs that are most often involved by **metastatic tumours**
• Primary carcinomas of the liver are relatively uncommon
• Most primary liver cancers arise from hepatocytes and are termed
- ➔ **Hepatocytes** → hepatocellular carcinoma.
- ➔ **Bile duct** (Much less common)→ Cholangiocarcinomas.
- ➔ **Other rare forms:** hepatoblastomas and angiosarcomas (mainly in children) .

Hepatocellular carcinoma (HCC)

Epidemiology

- Most common **primary liver malignancy**
- There is a clear predominance of males with a ratio of 2.4 : 1
- Peak incidence is between 20 & 40 years of middle age
- More than 85% of cases of HCC occur in countries with high rates of chronic hepatitis B virus **(HBV) infection**
- In the Western world where HBV is not prevalent, cirrhosis is present in 85% to 90% of cases of HCC, usually in the setting of other chronic liver diseases
- Primary carcinomas of the liver are relatively uncommon in North America and western Europe
- Incidence is highest in Asia (southeast China, Korea, Taiwan) & sub- Saharan Africa
- In these regions, the HBV carrier state begins in infancy following vertical transmission of virus from infected mothers, conferring a 200-fold increased risk for HCC by adulthood
- Rarely manifests before 60 years of age, and in almost 90% of cases the malignancy emerges after cirrhosis becomes established
- The third most frequent cause of cancer deaths
- In ~50% of cases, it arises in non-cirrhotic livers
- Accounts for approximately 5.4% of all cancers

HCC cont

Etiology

Five major etiologic factors associated with HCC have been established:

1. Chronic viral infection (HBV, HCV): More than 85% of cases of HCC occur in countries with high rates of chronic HBV infection

2.Cirrhosis: the development of cirrhosis appears to be an important, but not requisite, contributor to the emergence of HCC

3. Chronic alcoholism

4. Non-alcoholic steatohepatitis (NASH)

5. Food contaminants (primarily aflatoxins)

- -Is a mycotoxin produced by Aspergillus species
- -Contaminates staple food crops in Africa and Asia (in "moldy" grains and peanuts).
- ★Metabolites are present in the urine of individuals who consume these foods, as are aflatoxin-albumin adducts in serum.
- ★These biomarkers identify populations at risk and have helped to confirm the importance of aflatoxin in hepatocarcinogenesis

❖ Any food that contain aflatoxins especially in Africa and Asia could be risk of HCC

Other HCC risk factors: "only in females slides"

1. Inherited disorders, particularly hereditary hemochromatosis, tyrosinemia and α1 AT deficiency, and to a lesser degree Wilson disease
2. Metabolic syndrome and its attendant obesity, diabetes mellitus, and NAFLD (uncommon)

Pathogenesis

"Only in Males slides"

❖ Cell death, hepatocyte replication, and inflammation, seen in all forms of chronic hepatitis, are believed to be main contributors to **DNA damage.**

❖ Poor regulation of hepatocyte replication can occur by point mutations or overexpression of specific cellular genes (such as β-catenin).

Gross Morphology

"only in females slides"

❖ **HCC may appear grossly as:**

1. Unifocal (usually one large) mass
2. Multifocal, widely distributed multiple nodules of variable size and shape
3. diffusely infiltrative cancer

❖ **Intrahepatic metastasis** by either vascular invasion or direct extension ➔ small satellite tumor nodules around a larger primary mass

❖ In advanced cases: vascular invasion of **hepatic venous system➔** extrahepatic metastasis

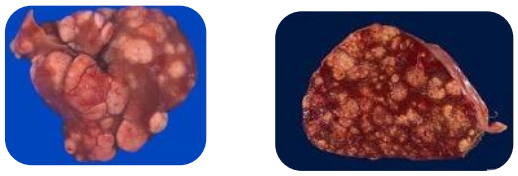
❖ Tumor may invade the **portal vein** (with occlusion of the portal circulation) or inferior vena cava, extending even into the right side of the heart

❖ **Lymph node** metastases to the perihilar, peripancreatic, and para-aortic nodes above and below the diaphragm can be present

❖ Occasionally, invades vascular channels ➔ long, snake-like masses of intravenous tumor
-Portal vein ➔ portal hypertension
-Inferior vena cava ➔ extend up to the heart (right ventricle)

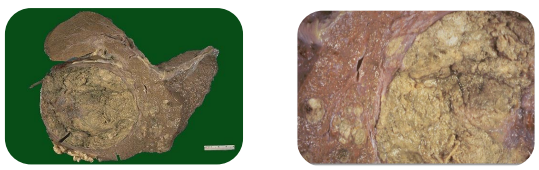
Unifocal nodule

Multifocal nodules
(greenish, or Whitish color caused by accumulation of bile

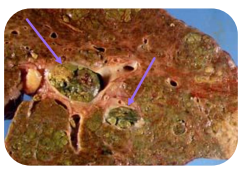


Large and bulky mass ,
has a greenish cast because it contains bile. To the right of the main mass are small satellite nodules

Metastases are usually small, satellite tumor nodules around a larger primary mass



Multiple nodules with **Venous invasion**

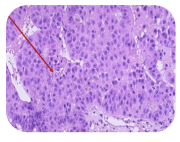


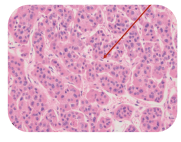
HCC cont.

Microscopic Morphology

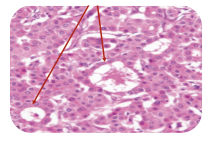
- Range from well-differentiated that are recognizable as hepatocytic in origin to highly anaplastic undifferentiated lesions.
- Neoplastic cells of well-differentiated HHCs are arranged in:
  - ➢ Thick trabeculae and Pseudoglands
- Bile pigment is usually present (intracellular bile)
- The malignant cells may be positive for alpha-fetoprotein

Thick trabeculae
Well differentiated



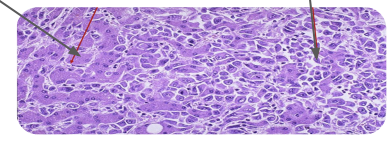


Pseudoglands

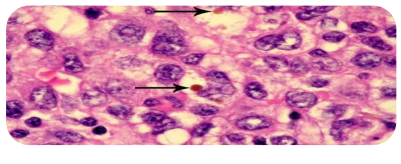


Larger hepatocytes

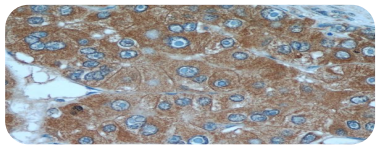
Well differentiated and interdigitate with normal



Intracellular bile pigment is usually present



The malignant cell may be **+ve alpha-fetoprotein**



Prognosis

"only in females slides"

- **Death occurs usually due to:**

1. Cachexia
2. Gastrointestinal or esophageal variceal bleeding
3. Liver failure with hepatic coma
4. Tumor rupture with fatal hemorrhage

- **Most common site of metastasis is LUNG**
- **Prognosis is very bad**; majority die within 2 years of Dx

HCC variant- Fibrolamellar carcinoma

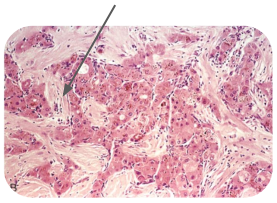
Introduction

- A distinctive variant of hepatocellular carcinoma.
- It occurs in young male and female adults (20 to 40 years of age) with equal incidence
- No underlying chronic liver diseases (HBV or cirrhosis)
- Constitutes 5% of HCCs

Morphology

- Composed of well-differentiated **polygonal cells growing in nests** or cords and separated by **parallel lamellae of dense collagen bundles**.
- **Single large, hard mass "scirrhous" tumor** , with **fibrous bands** coursing through it.
- The tumor cells have abundant eosinophilic cytoplasm and prominent nucleoli

Bands of lamellar fibrosis



Clinical Features

- Ill-defined upper abdominal pain,
- Malaise, fatigue, weight loss (general symptoms) , and feeling of abdominal fullness
- Clinical examination : In many cases, the enlarged liver can be felt on palpation.
- Jaundice and fever are uncommon
- **Laboratory studies: Elevated levels of serum α-fetoprotein** are found in 50% to 75% of patients with HCC

Prognosis

- Better prognosis than the conventional HCC

Cholangiocarcinoma

Cholangio: bile duct

Introduction

- Second most common primary malignant tumor of liver
- Is a malignancy of the biliary tree, Arises from intrahepatic or extrahepatic bile ducts
  - 50% to 60% of all CCAs are perihilar (Klatskin) tumors
  - 20% to 30% are distal tumors
  - 10% are intrahepatic

Risk factors

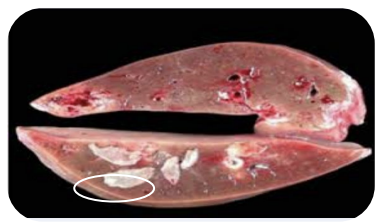
- Congenital fibropolycystic diseases of the biliary system (particularly Caroli disease and choledochal cysts)
- Previous exposure to certain toxin such as Thorotrast : (formerly used in radiography of the biliary tract)
- In the Orient region , the incidence rates are higher, and it is due to chronic infection of the biliary tract by the liver fluke Opisthorchis sinensis
- Chronic inflammatory disease of large bile ducts (such as primary sclerosing cholangitis, IBD), hepatolithiasis & fibropolycystic liver disease. All → cholestasis & chronic inflammation
- As with HCC, rates also are elevated in patients with hepatitis B and C and NAFLD

Gross finding of Extrahepatic

"only in females slides"

- Small lesions & discovered early due to obstruction of biliary tract
- Firm, gray nodules within the bile duct wall
- Can be diffusely infiltrative lesions
- Papillary, polypoid lesions
- Most are adenocarcinomas

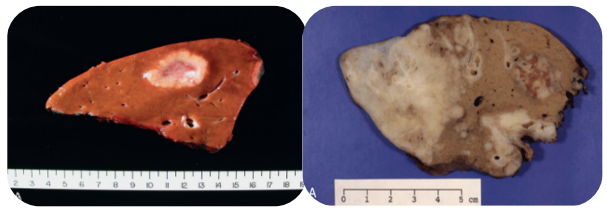
liver fluke



Gross finding of Intrahepatic

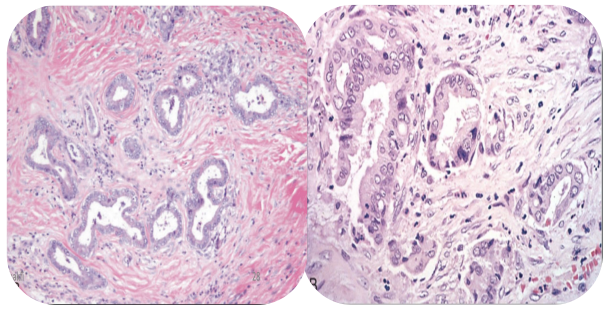
"only in females slides"

- Occur in the noncirrhotic liver
- Track along the intrahepatic portal tract system to create a treelike tumorous mass within a portion of the liver



Microscopic finding

- Typically are mucinous- producing **adenocarcinomas**
- Intrahepatic cholangiocarcinomas resemble adenocarcinomas arising in other parts of the body, Most are well to moderately differentiated
- Well differentiated : can produce glands
- Poorly differentiated : there is no glands
- Abundant fibrous stroma (desmoplastic stroma)
- Common lymphovascular & perineural invasion
- Extensive extrahepatic & intrahepatic metastasis
- Cholangiocarcinomas are rarely bile stained, because differentiated bile duct epithelium does not synthesize bile

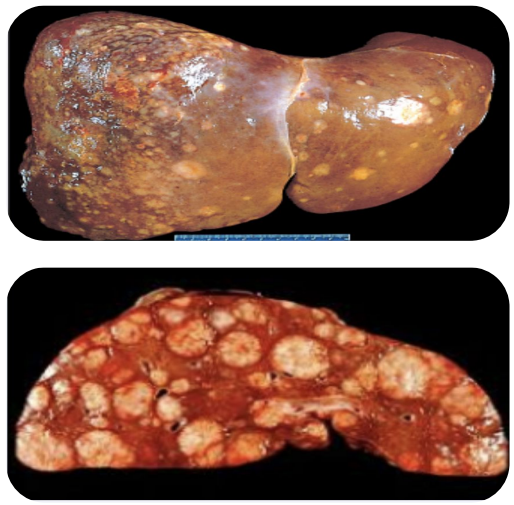


Clinical Picture & Prognosis

- Intrahepatic CCAs are not usually detected until late in their course and come to the attention because of obstruction of bile flow, or as a symptomatic liver mass
- Hilar and distal tumors present with symptoms of biliary obstruction, cholangitis, and right upper quadrant pain
- **Prognosis is poor** with survival rates of about 15% at 2 years after diagnosis
- The median time from diagnosis to death for intrahepatic CCAs is 6 months, even after surgery
- Alpha-fetoprorein is not elevated

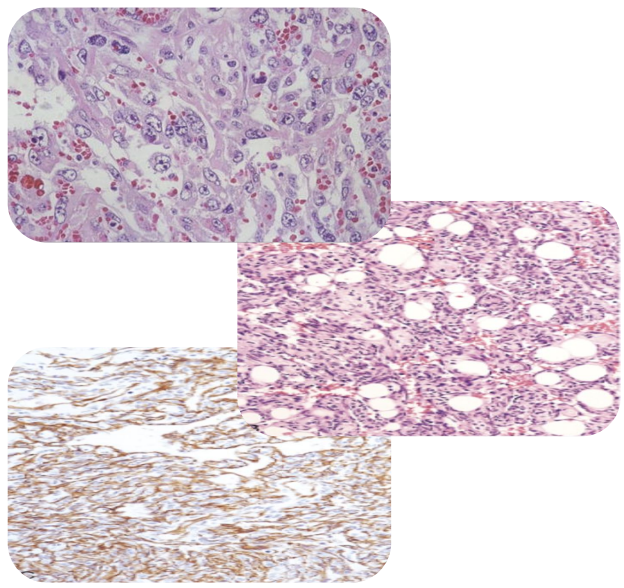
Metastatic Tumors

- Far more common than primary neoplasia
- Most common primaries producing hepatic metastases are those of the breast, lung, and colon, any cancer in any site of the body may spread to the liver, including leukemias and lymphomas
- **Multiple nodular metastases are found** that often cause striking hepatomegaly and may replace over 80% of existent hepatic parenchyma. The liver weight can exceed several kilograms

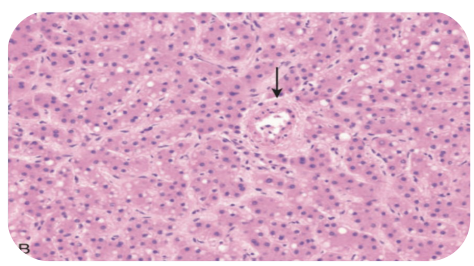


Other Malignant tumors: Angiosarcoma

- Malignant pleomorphic endothelial cells with large hyperchromatic nuclei, giant cells in frequent mitosis and irregular anastomosing vascular channels. The cells may appear spindle shaped
- Any site of the body that have blood vessels can have Angiosarcoma and hemangioma
- Cirrhosis is present in 20% to 40% of the cases
- These have also been linked to vinyl chloride and thorotrast exposure

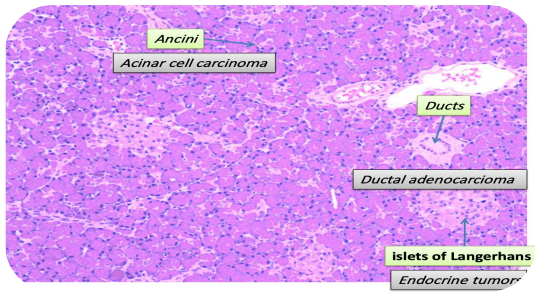


Benign Hepatic Tumors: Hepatocellular Adenomas

General information	❖ Benign neoplasms developing from hepatocytes, occurs as a solitary, sharply demarcated mass up to 40 cm ❖ Risk factor : Sex hormone (**oral contraceptive pills** & anabolic steroids) exposure ➔ markedly increases frequency of occurrence ❖ Cessation of exposure to sex hormones often “but not always” ➔ tumor regression ❖ The most common symptom is pain, occasionally rupture, an event that may lead to life-threatening intra-abdominal bleeding ❖ In about 30% of patients, the tumor tends to bleed into the peritoneal cavity, inducing hypovolemic shock that requires emergency treatment.
Molecular Subclassification “only in females slides”	❖ Low risk for malignant transformation ❖ Intermediate risk for malignant transformation ❖ High risk for malignant transformation
Microscopic “only in females slides”	Cords of hepatocytes, with an arterial vascular supply (arrow) and no portal tracts 

Pancreatic Carcinoma

Introduction



Acini ; Acinar cell carcinoma
Ducts ; Ductal cell carcinoma (most common)
islets of langerhan ; Endocrine tumors

Epidemiology

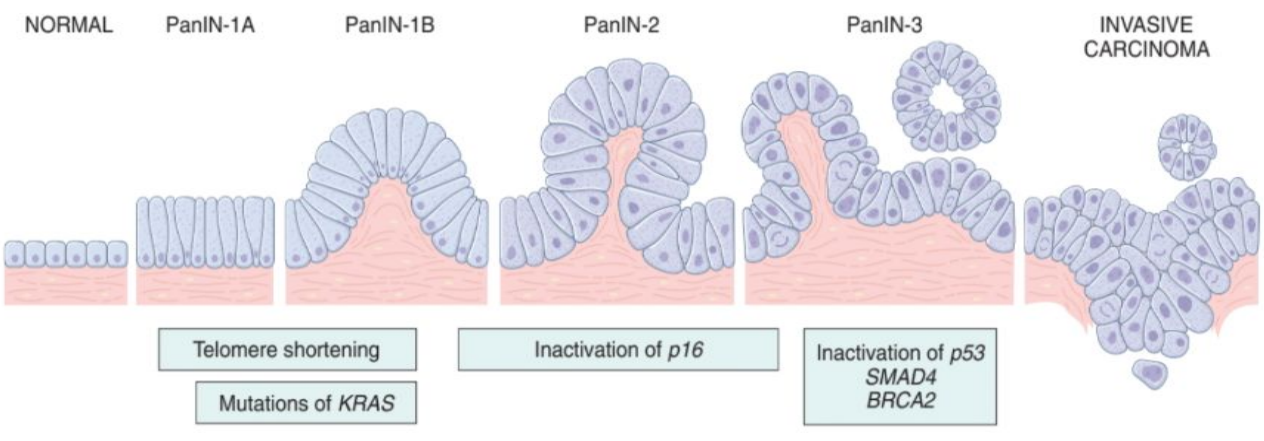
- Pancreatic cancer has one of the highest mortality rates of any cancer. It is carcinoma of the exocrine pancreas. It arises from ductal epithelial cells
- 80% in persons 60-80 years of age
- It is more common in blacks than in whites, diabetics more than non-diabetics.
- Males more than females
- Fourth leading cause of cancer deaths in the United States, preceded only by lung, colon, and breast cancers

Etiology

- The strongest environmental influence is **SMOKING** (major risk factor)
- Long-standing **chronic pancreatitis and DM**
- Familial clustering, e.g. **germline mutation** of familial breast/ovarian cancer **gene BRCA2** are seen in 10% of cases

Pathogenesis

- Arises from **precursor lesions** Pancreatic intraepithelial neoplasia **(PanINs)** as result of progressive accumulation of inherited & acquired genetic mutations in pancreatic epithelium
- A K-RAS mutation is an early event in pancreatic carcinogenesis

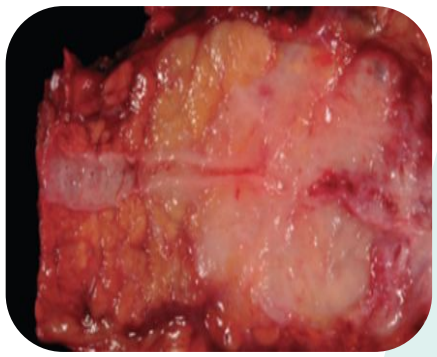


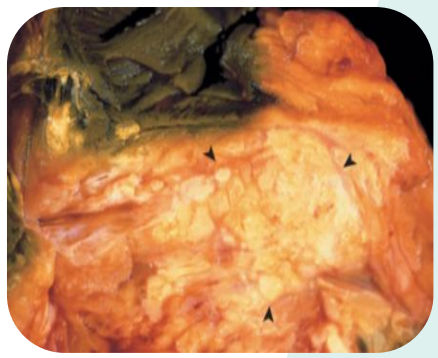
- Four genes are most affected by somatic (acquired) mutations in this neoplasm:
  - **KRAS,**
  - **CDKN2A/p16,**
  - **SMAD4**
  - **TP53**

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. (Modified from Maitra A, Hruban RH: Pancreatic cancer, Annu Rev Pathol Mech Dis 3:157, 2008.)

Macro and Microscopic findings



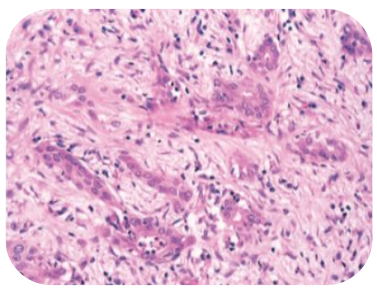


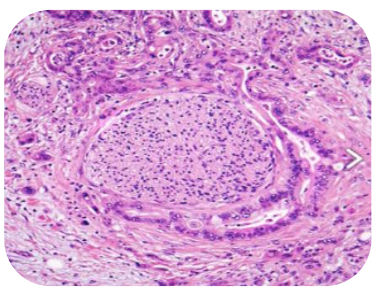
1 Gross:

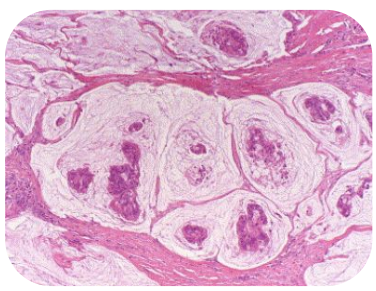
- Approximately 60% of cancers of the pancreas arise in the **head** of the gland, 15% in the body, and 5% in the tail; in 20%, the neoplasm diffusely involves the entire gland
- 5 % in the tail
- Hard, gray-white, stellate, poorly defined masses

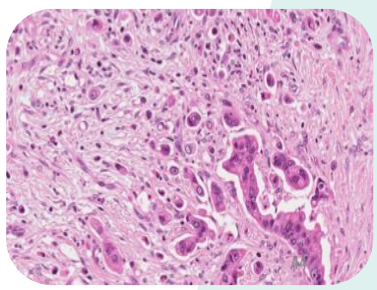
2 Microscopic:

- Majority of carcinomas are ductal adenocarcinomas.
- Two characteristic features:
  - Have prominent desmoplastic (stromal fibrosis) response
  - Highly invasive; often have invaded surrounding structures even early
- Prominent perineural invasion & common lymphatic invasion
- Peripancreatic, gastric, mesenteric, omental, and portahepatic lymph nodes are frequently involved. Distant metastases occur, principally to the lungs and bones









Less common variant forms of pancreatic cancer include :

- **Adenosquamous carcinoma**
- **Colloid carcinoma**
- **Hepatoid carcinoma**
- **Medullary carcinoma**
- **Signet-ring cell carcinoma**
- **Undifferentiated carcinoma**
- **Undifferentiated carcinomas with osteoclast-like giant cells**

Clinical picture

- Remain silent until they invade into adjacent structures → (**1st symptom)** Erode the nerve fibers in retroperitoneum lead to pain

- Tumors of the **head** of pancreas leads obstructive jaundice (**Painless jaundice** is a frequent initial symptom of pancreatic cancer)
- Signs of advanced disease:
  - Jaundice Wt. loss, anorexia, generalized malaise & weakness
- Migratory thrombophlebitis (Trousseau sign,) occurs in about 10% of patients due to platelet-aggregating factors and procoagulants from the carcinoma or its necrotic products

Prognosis "only in females slides"

- The clinical course of pancreatic carcinoma is rapidly progressive
- Less than 20% of pancreatic cancers are resectable at the time of diagnosis.
- 5-year survival is < 5%

This summary was taken from Robbins

Summary

Liver tumors

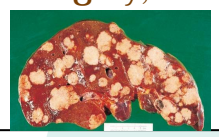
- The liver is the most common site of metastatic cancers from primary tumors of the colon, lung, and breast.
- Hepatocellular adenomas are benign tumors of hepatocytes.
- Most can be subclassified on the basis of molecular changes with varying degrees of malignant potential.
- They are associated with use of oral contraceptives and androgens
- The two main types of malignant tumors are hepatocellular carcinomas and cholangiocarcinomas; HCCs are much more common.
- HCC is a common tumor in regions of Asia and Africa, and its incidence is increasing in the United States.
- The main etiologic agents for HCC are hepatitis B and C, alcoholic cirrhosis, hemochromatosis, and exposure to aflatoxins. In the Western population, about 90% of HCCs develop in cirrhotic livers; in Asia, almost 50% of cases develop in noncirrhotic livers.
- chronic inflammation and cellular regeneration associated with viral hepatitis are predisposing factors for the development of carcinomas.
- HCC may be unifocal or multifocal, tends to invade blood vessels, and recapitulates normal liver architecture to varying degrees.
- Cholangiocarcinoma is a tumor of intrahepatic or extrahepatic bile ducts that is relatively common in areas where liver flukes, such as Opisthorchis and Clonorchis species, are endemic.

Pancreatic tumors

- Pancreatic cancer probably arises from noninvasive precursor lesions (most commonly, PanINs), developing by progressive accumulation of mutations of oncogenes (e.g., KRAS) and tumor suppressor genes (e.g., CDKN2A/p16,TP53, and SMAD4).
- Typically, these neoplasms are ductal adenocarcinomas that produce an intense desmoplastic response.
- Most pancreatic cancers are diagnosed at an advanced stage, accounting for the high mortality rate.
- Obstructive jaundice is a feature of carcinoma of the head of the pancreas; many patients also experience debilitating pain.
- Carcinomas of the tail of the pancreas are often not detected until late in their course.

QUIZ!

MCQs

01 | Which of the following is the most common primary liver malignancy?			
A) Hepatoblastomas	B) Angiosarcomas	C) Cholangiocarcinomas	D) Hepatocellular Carcinoma (HCC)
02 | well-differentiated polygonal cells growing in nests or cords and separated by parallel lamellae of dense collagen bundles, best describes?			
A) Fibrolamellar carcinoma	B) Hepatic adenoma	C) Pancreatic carcinoma	D) Cholangiocarcinoma
03 | A 69-year-old woman arrives in the emergency room complaining of weakness, abdominal pain, and a 9 kg (20 lb) weight loss during the past month. Physical examination reveals jaundice, conspicuous hepatomegaly, and ascites. The patient expires, and a section of liver is examined at autopsy (shown in the image). Which of the following is the most likely diagnosis? 			
A) Hemangiosarcoma of the liver	B) Metastatic carcinoma of the liver	C) Primary hepatocellular carcinoma	D) Sarcoidosis
04 | A 52-year-old recent immigrant from Vietnam complains of abdominal swelling, weight loss, and upper abdominal pain of 3 weeks in duration. His past medical history includes malaria and infection with the liver fluke Clonorchis sinensis. The liver is hard to palpation. An abdominal CT scan shows a hypoat- tenuated mass with lobulated margins in the liver. A biopsy discloses well-differentiated neoplastic glands embedded in a dense fibrous stroma. Which of the following is the most likely diagnosis?			
A) Hepatocellular carcinoma	B) Cholangiocarcinoma	C) Hepatocellular carcinoma	D) Metastatic colon adenocarcinoma
05 | Which one of the following is associated with high level of alpha fetoprotein			
A) Pancreatic Carcinoma	B) Angiosarcoma	C) Cholangiocarcinoma	D)Hepatocellular carcinoma
06 | which one of the following gene is mostly mutated in case of familial pancreatic carcinoma X			
A) BRCA2	B) KRAS	C) TP53	D) CDKN2A/p16

MCQs Answer key	01	02	03	04	05	06
	D	A	B	B	D	A

" اللهم علمنا ماينفعنا ، وانفعنا بما علمتنا وزدنا علما يارب العالمين "

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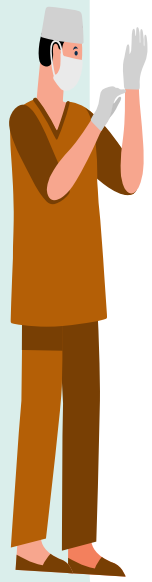

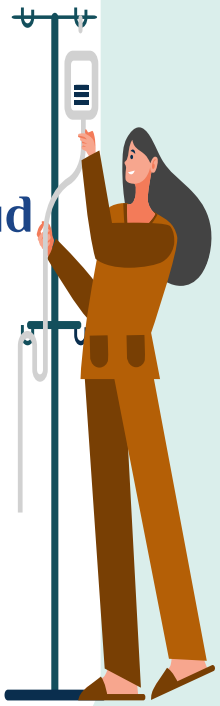

This Lecture done by

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