

# GIT Module, Pathology

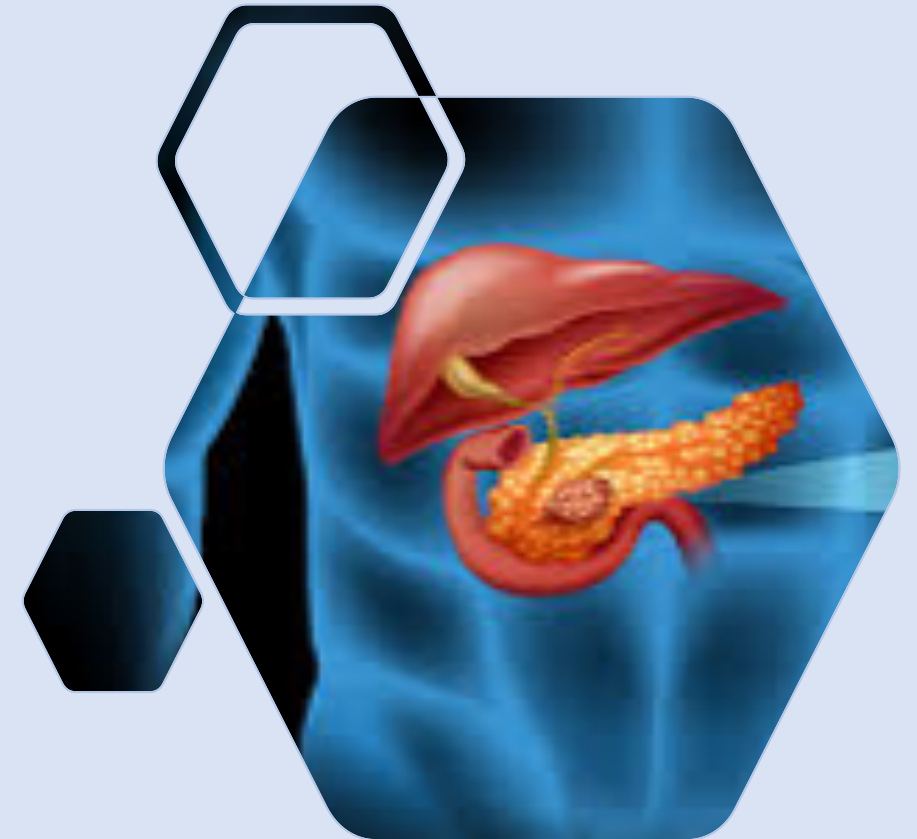
## LIVER AND PANCREAS NEOPLASM

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# Objectives

- Introduction
- Describe most common liver malignancies
  - 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

# Introduction

- 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
  - ✓ Hepatocellular carcinoma (HCC)
  - ✓ Much less common are carcinomas of bile duct origin, cholangiocarcinomas
  - ✓ Rare forms of primary liver cancer : hepatoblastomas and angiosarcomas

## Benign

- Cavernous Hemangiomas
- Hepatocellular Adenomas

## Malignant

- Metastases\*  
“Most common liver tumor”
- Primary tumors:
  - ✓ Hepatocellular Carcinoma
  - ✓ Cholangiocarcinoma
  - ✓ Hepatoblastoma “rare”
  - ✓ Angiosarcoma “rare”



# Hepatocellular Carcinoma (HCC)

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# Hepatocellular Carcinoma (HCC)

- Most common 1ry liver malignancy
- Accounts for approximately 5.4% of all cancers
- 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
- Peak incidence is between 20 & 40 years of age middle age

# Hepatocellular Carcinoma (HCC)

- More than 85% of cases of HCC occur in countries with high rates of chronic HBV infection.
- 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

# Hepatocellular Carcinoma (HCC)

- Rarely manifests before 60 years of age, and in almost 90% of cases the malignancy emerges after cirrhosis becomes established
- There is a clear predominance of males with a ratio of 2.4 : 1
- The third most frequent cause of cancer deaths
- In ~50% of cases, it arises in non-cirrhotic livers

# Pathogenesis

**Four major etiologic factors associated with HCC have been established:**

1. Chronic viral infection (HBV, HCV)
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 that
  - ✓ Contaminates staple food crops in Africa and Asia.
  - ✓ 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

# Pathogenesis

## **Other HCC risk factors:**

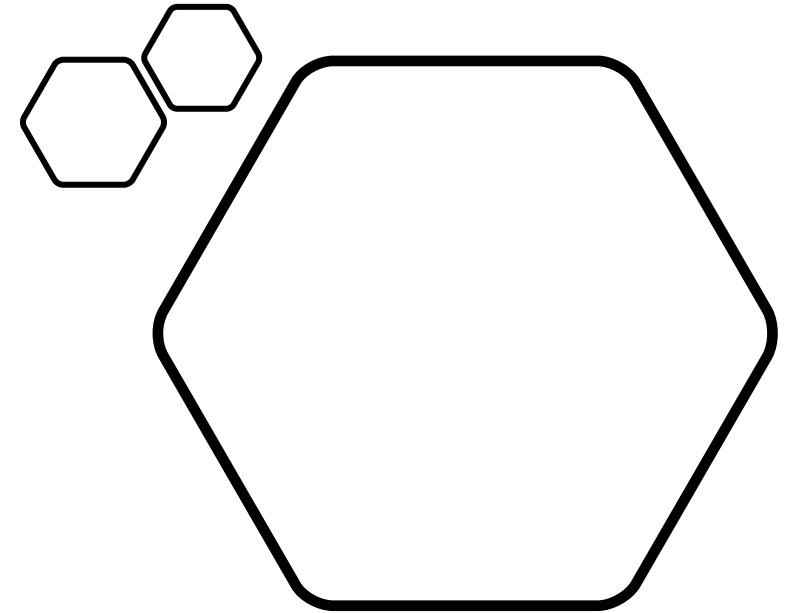
1. Inherited disorders, particularly hereditary hemochromatosis, tyrosinemia and  $\alpha$ 1 AT deficiency, and to a lesser degree Wilson disease
2. Metabolic syndrome and its attendant obesity, diabetes mellitus, and NAFLD.

# HCC

## Gross morphology

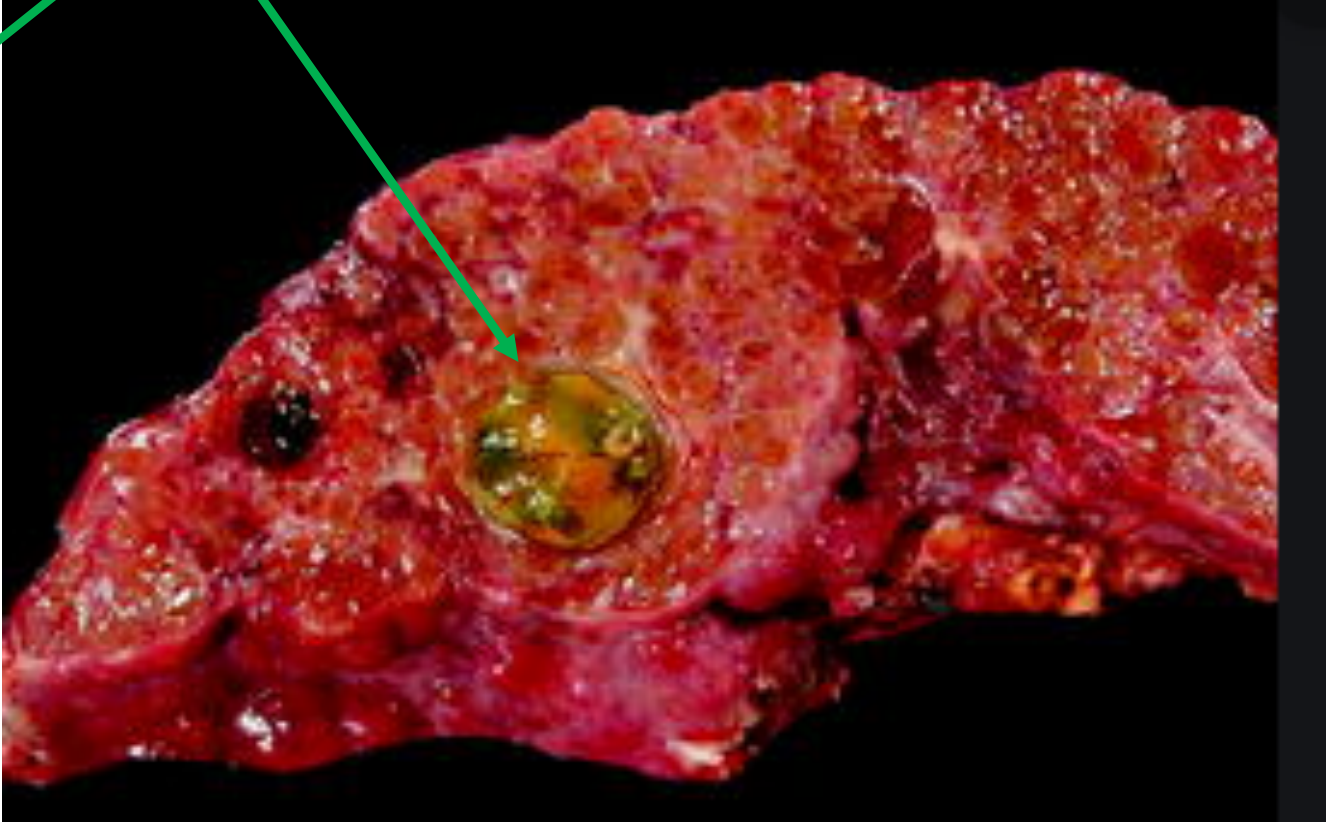
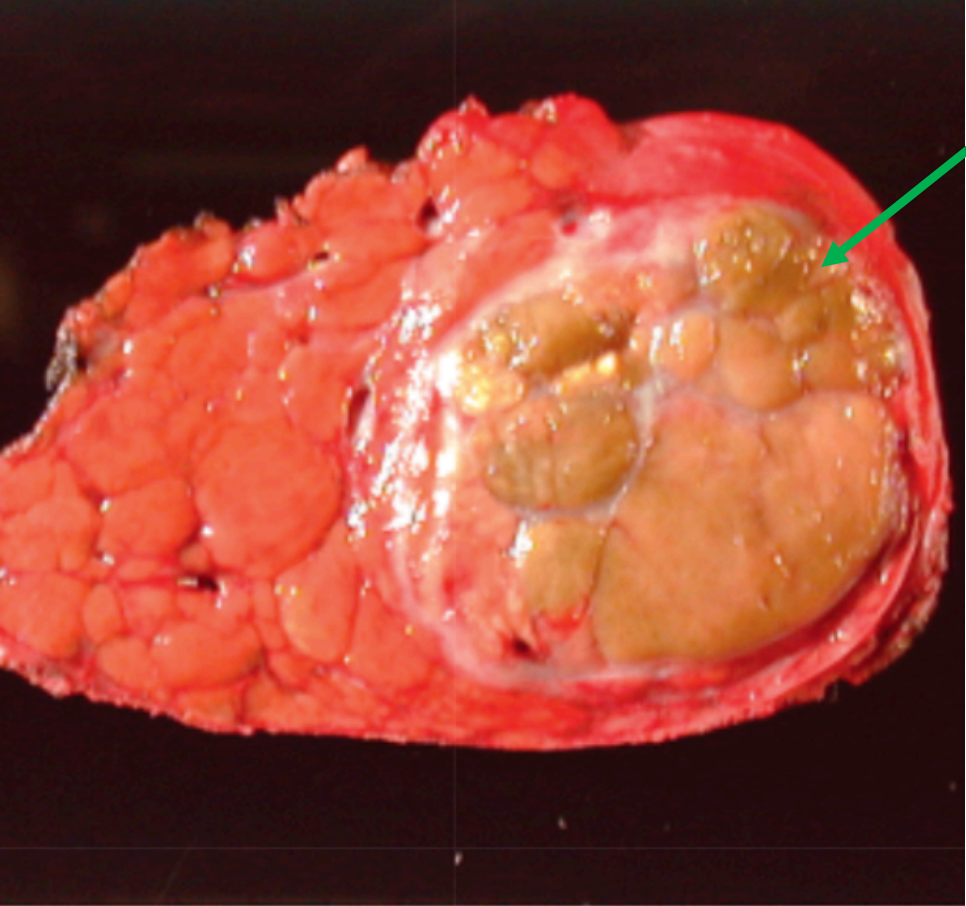
- **HCC may appear grossly as:**

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



# HCC- Gross Morphology

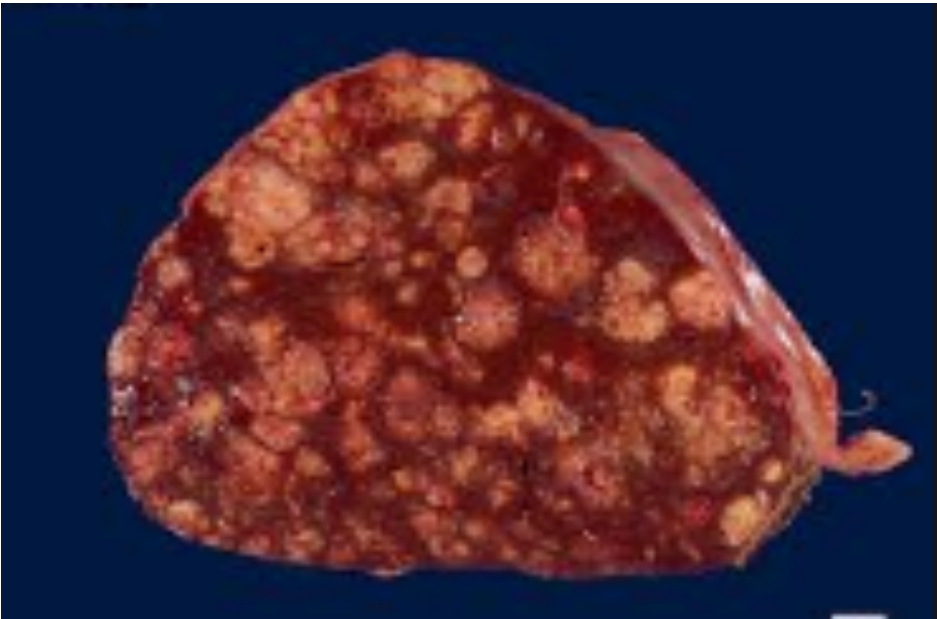
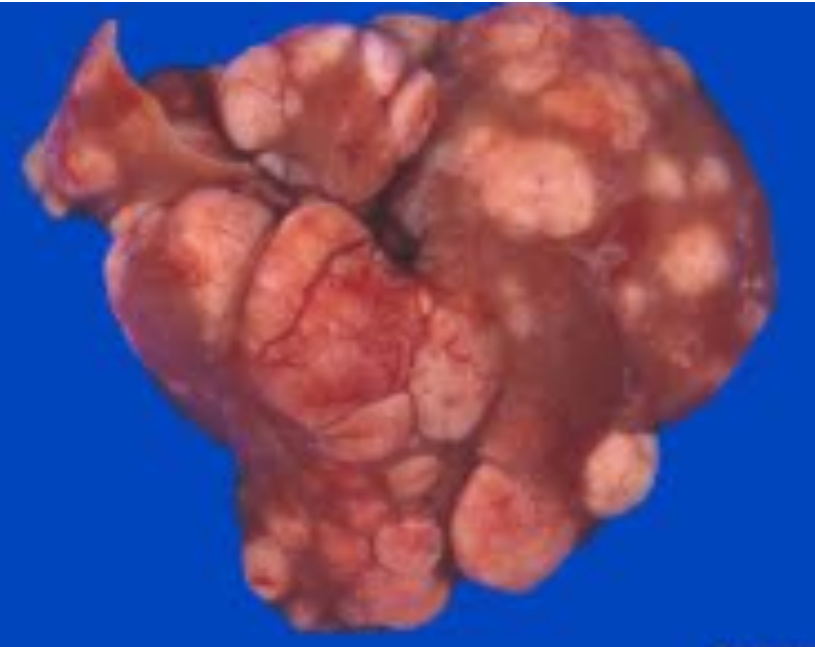
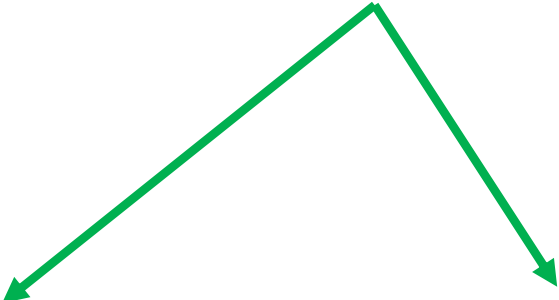
Unifocal nodule





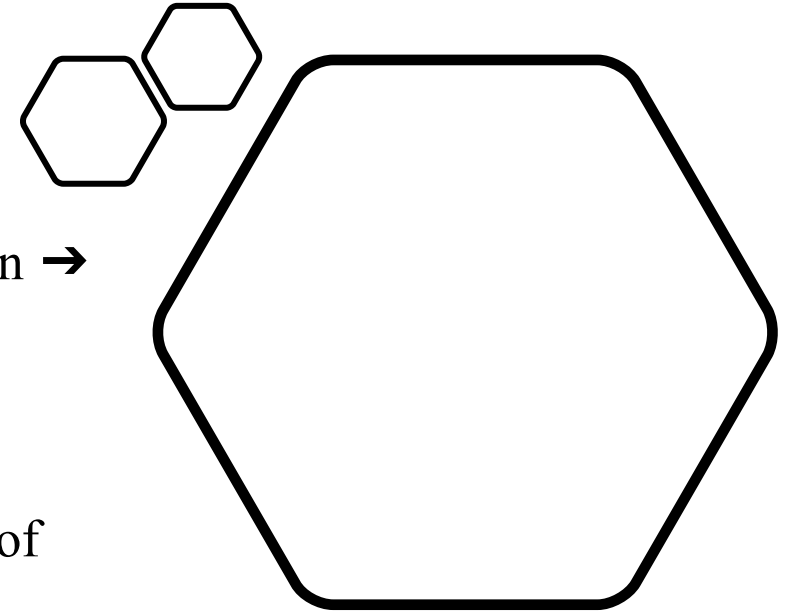
# HCC- Gross Morphology

Multifocal nodules

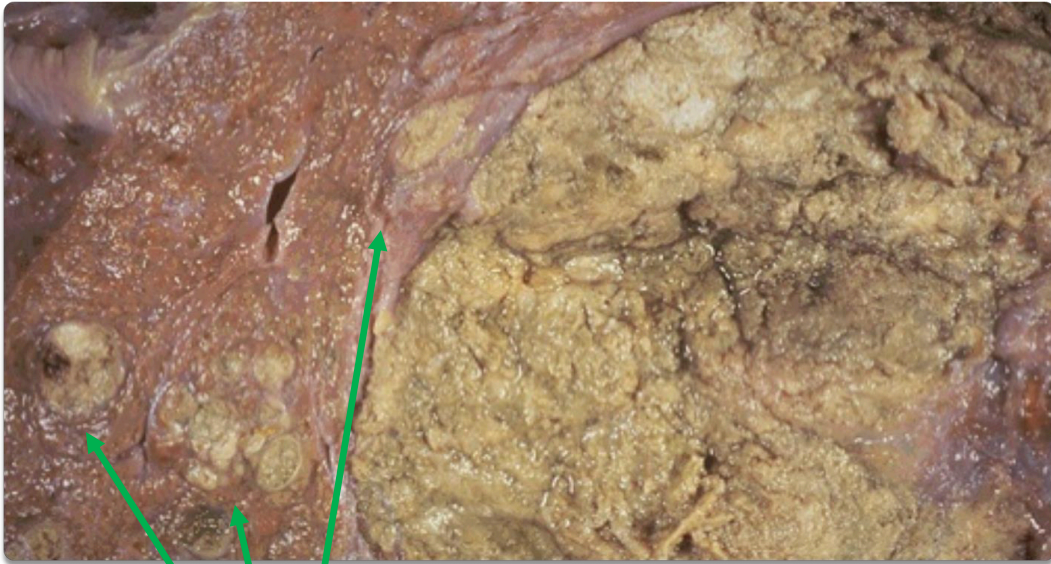


# HCC- Morphology

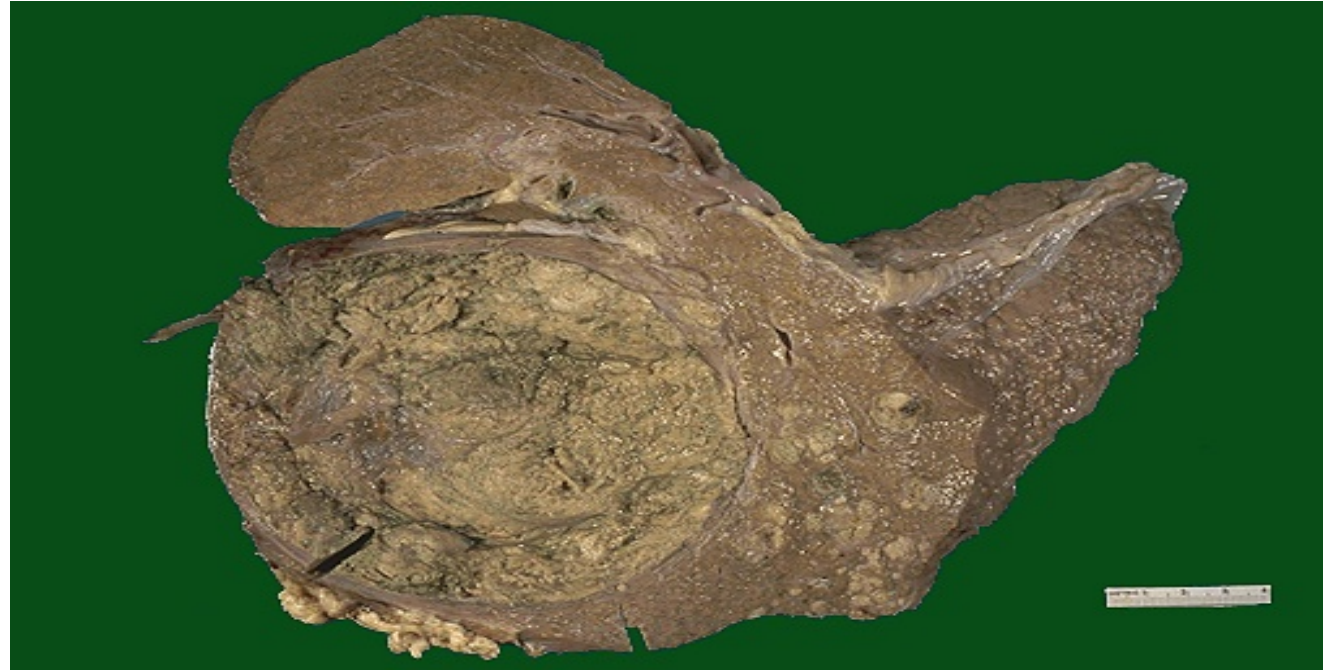
- Intrahepatic metastasis by either vascular invasion or direct extension → small satellite tumor nodules around a larger primary mass
- In advanced cases: vascular invasion of hepatic venous system → extrahepatic metastasis
- Tumor may invade the portal vein (with occlusion of the portal circulation) 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.
- Hepatocellular carcinomas range from well-differentiated to highly anaplastic undifferentiated lesions.
- 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)



# HCC- Gross Morphology



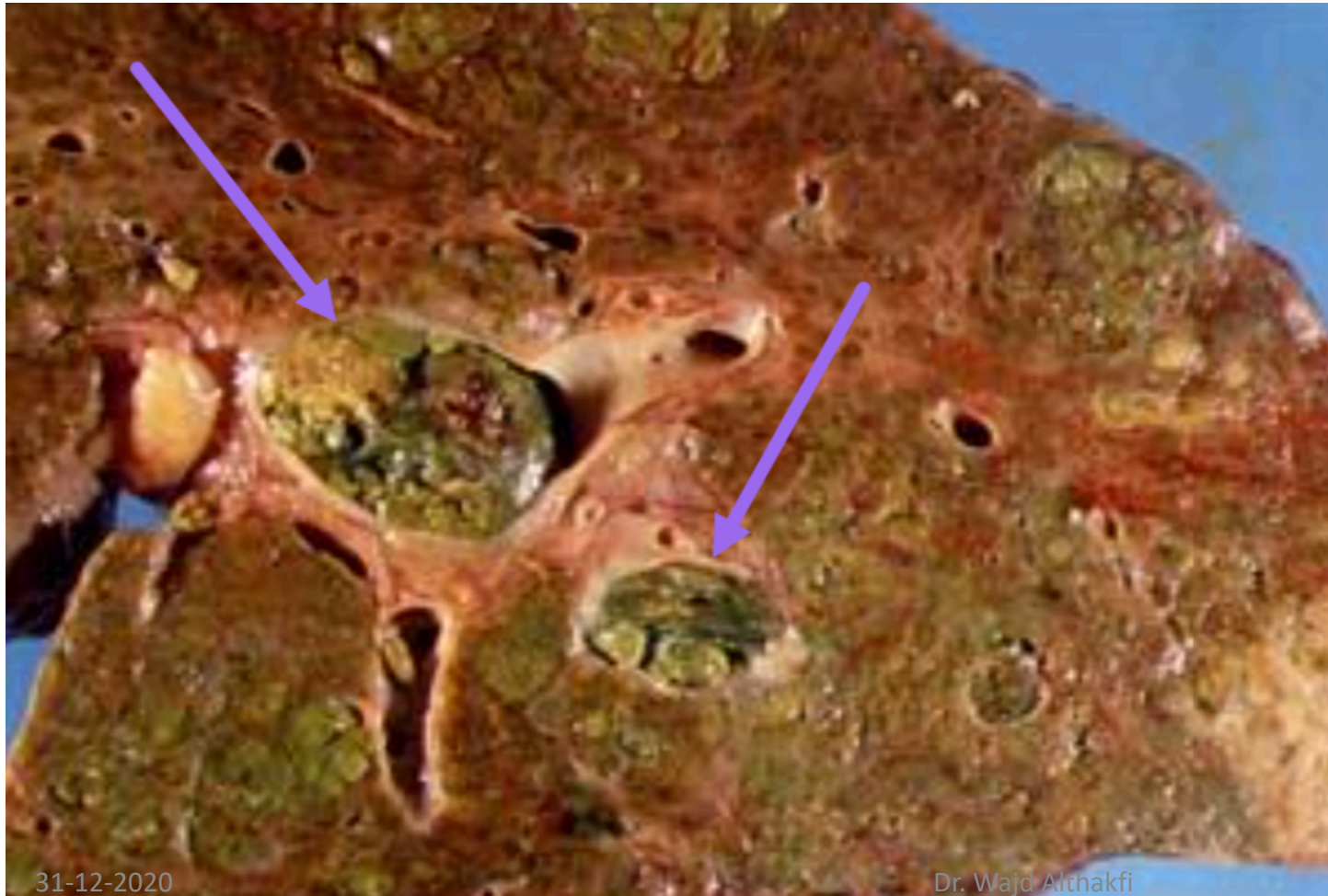
Metastases are usually small, **satellite tumor** nodules around a larger primary mass



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



# HCC- Gross Morphology

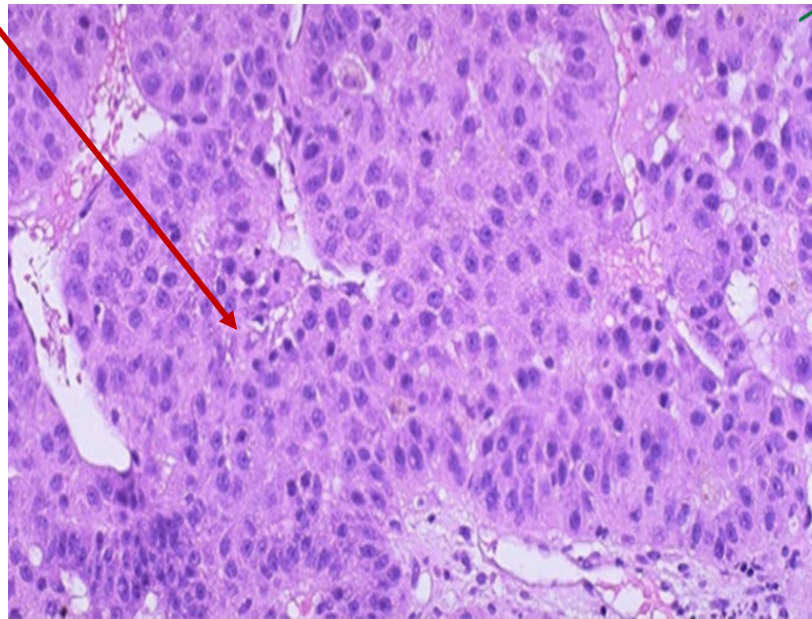
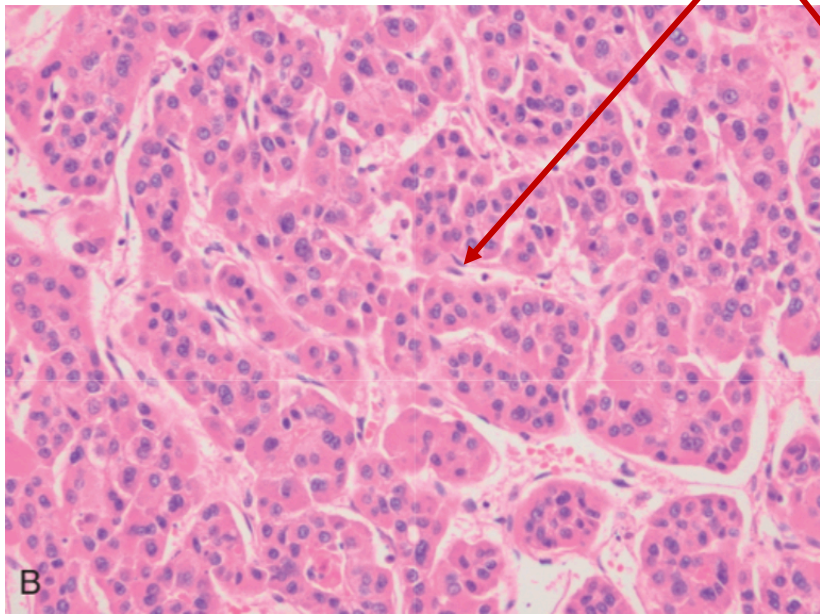


**Venous invasion**

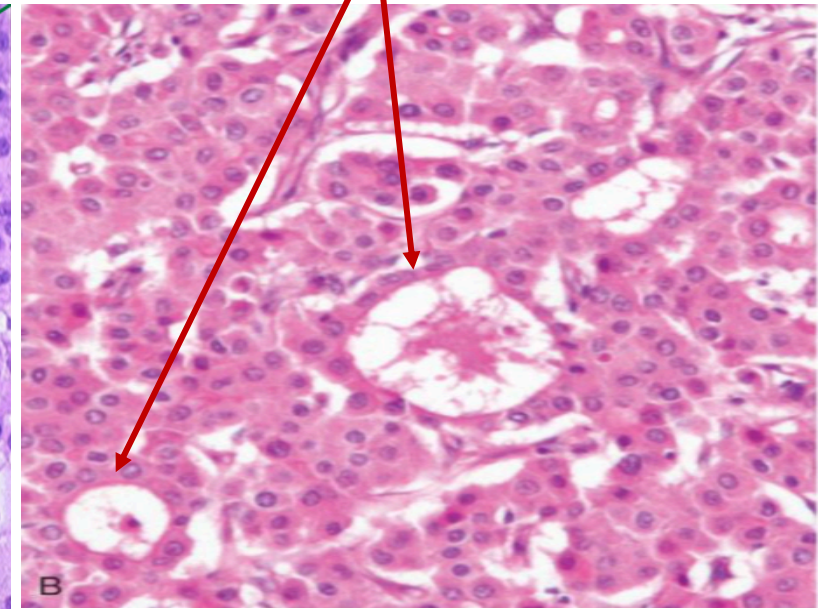
# HCC- Microscopic

- Range from well-differentiated to highly anaplastic undifferentiated lesions.
- Neoplastic cells of well-differentiated HCCs are arranged in:

*Thick trabeculae*



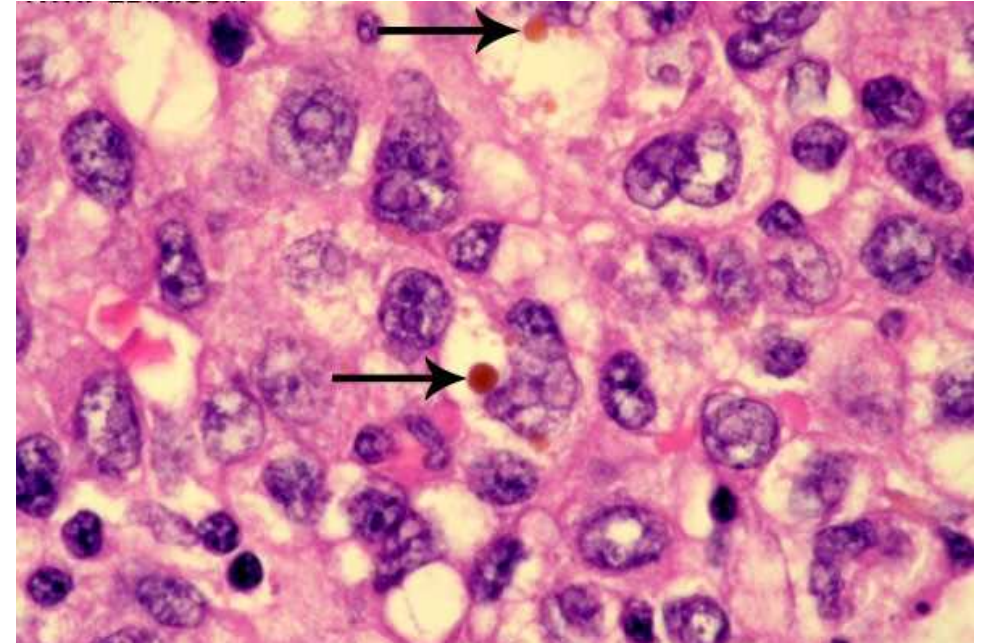
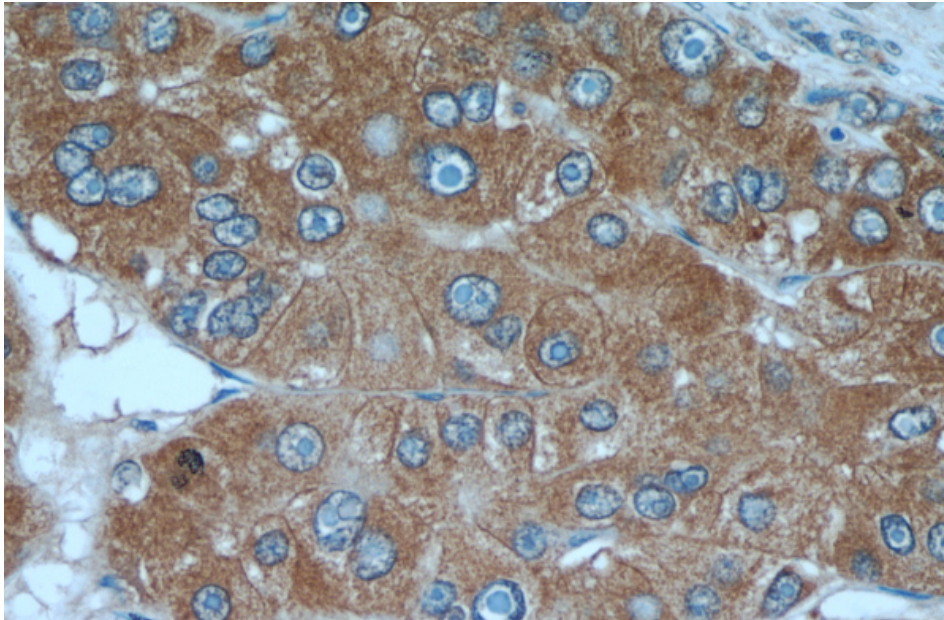
*Pseudoglands*





# HCC- Microscopic

**Bile pigment is usually present**



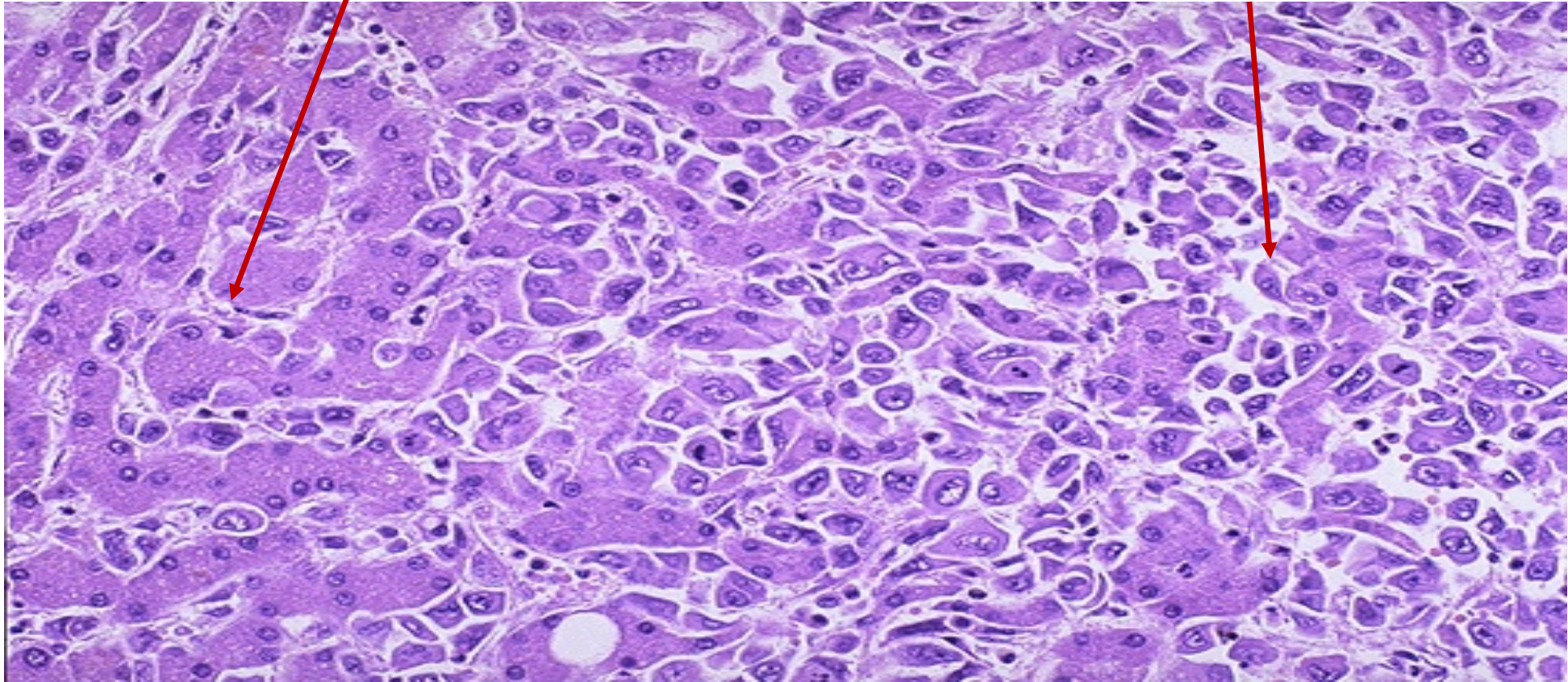
**The malignant cells may be positive for alpha-fetoprotein**



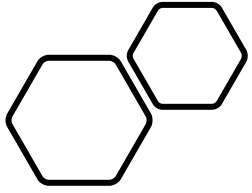
# HCC- Microscopic

**HHC are well differentiated and interdigitate with normal**

**Larger hepatocytes**

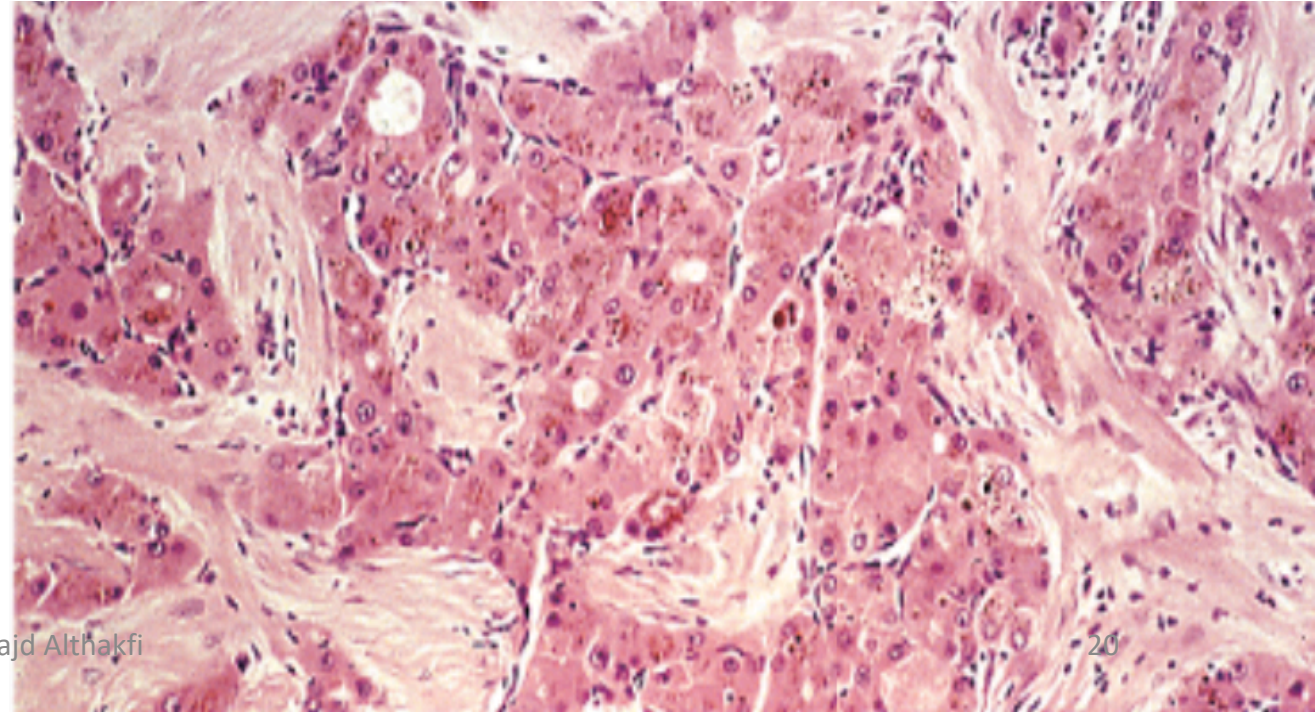






## HCC variant- Fibrolamellar carcinoma

- Constitutes 5% of HCCs
- It occurs in young male and female adults (20 to 40 years of age) with equal incidence
- No underlying chronic liver diseases
- Better prognosis than the conventional HCC
- Morphology:
  - ✓ Single large, hard “scirrhus” tumor with fibrous bands coursing through it
  - ✓ composed of well-differentiated polygonal cells growing in nests or cords and separated by parallel lamellae of dense collagen bundles
  - ✓ The tumor cells have abundant eosinophilic cytoplasm and prominent nucleoli





# Fibrolamellar carcinoma

## Clinical Features

- Ill-defined upper abdominal pain, malaise, fatigue, weight loss, and feeling of abdominal fullness
- In many cases, the enlarged liver can be felt on palpation. Jaundice and fever are uncommon
- Laboratory studies: Elevated levels of serum  $\alpha$ -fetoprotein are found in 50% to 75% of patients with HCC

# HCC – Prognosis

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



# **Cholangiocarcinoma (CCA)**

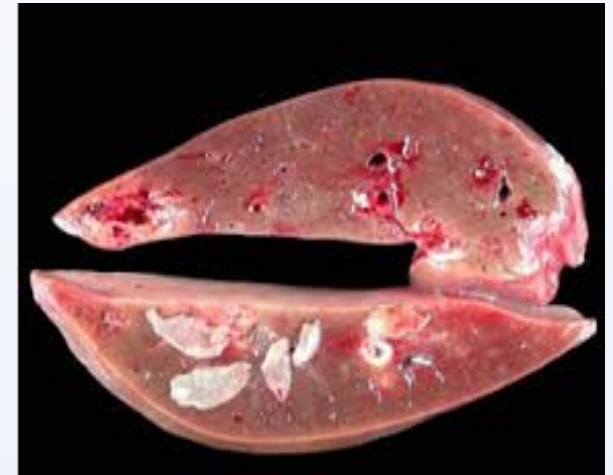
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# Cholangiocarcinoma

- 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

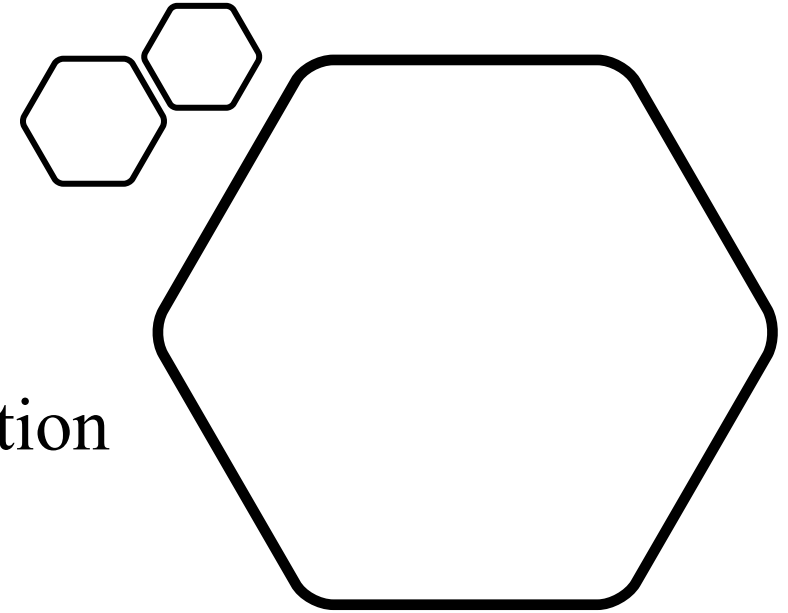
# CCA- Risk factors

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



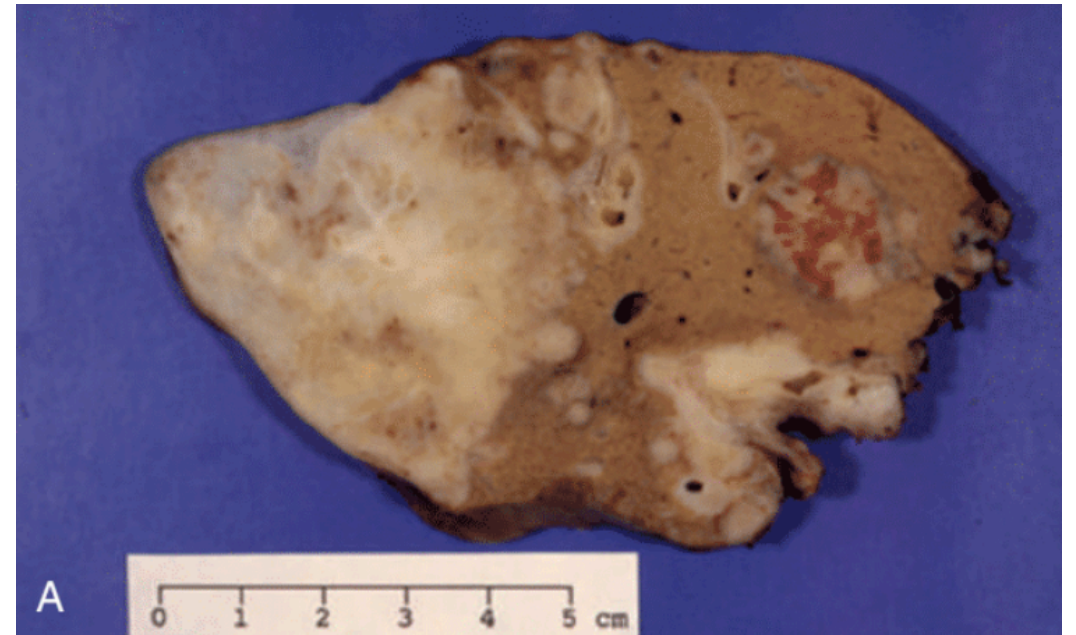
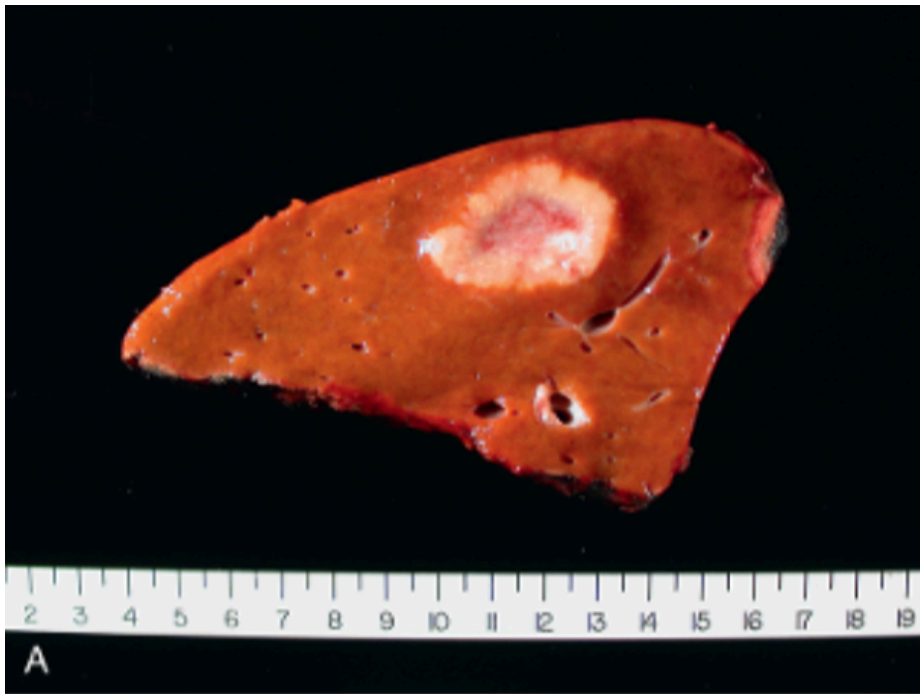
# Gross finding of Extrahepatic CCA

- 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



# Gross finding of Intrahepatic CCA

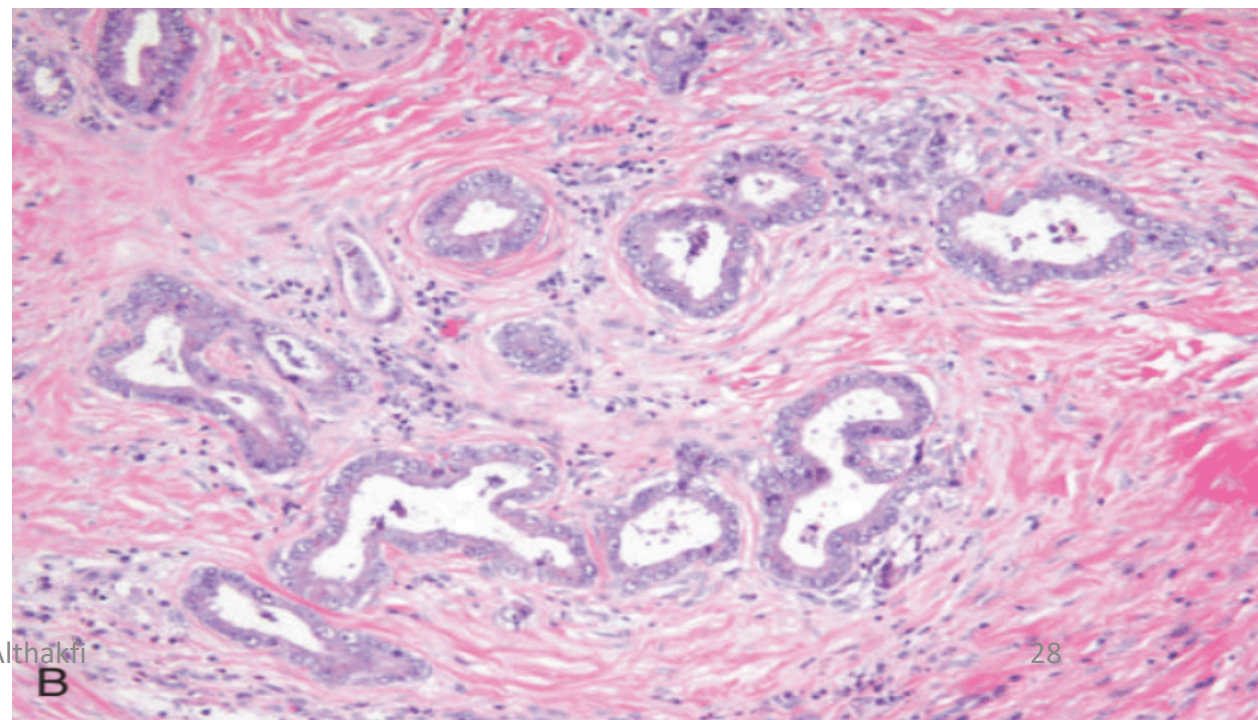
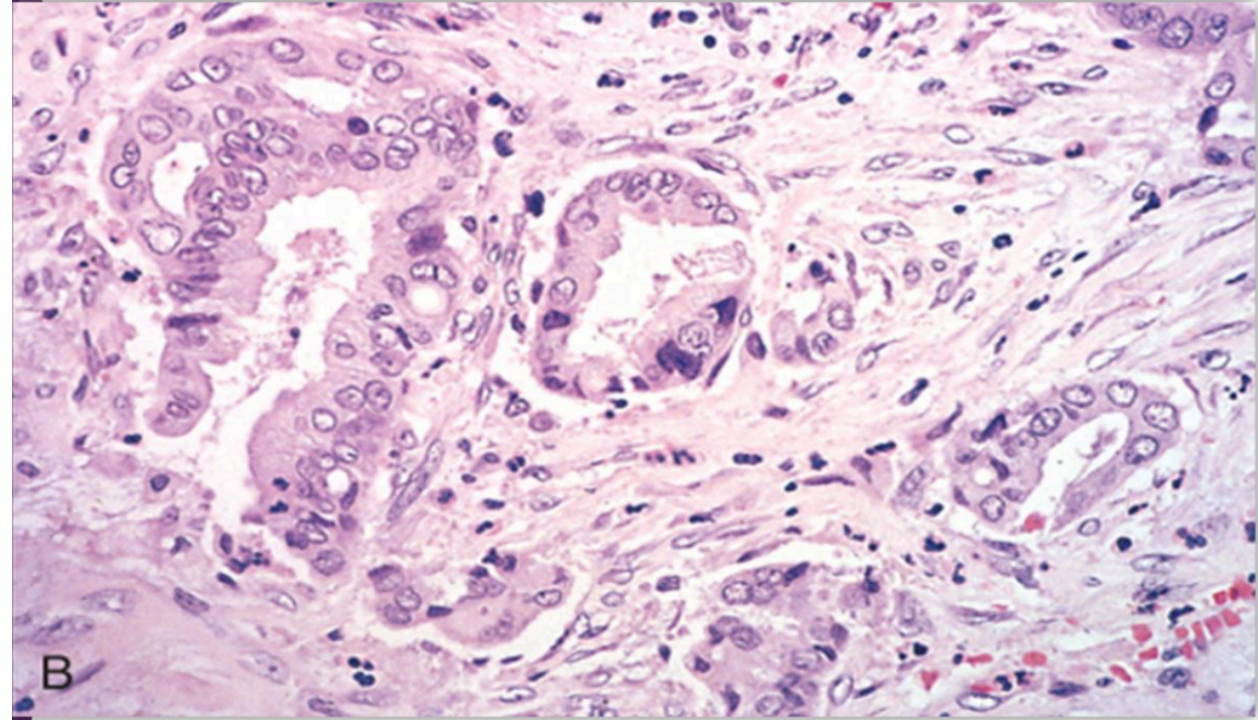
- Occur in the noncirrhotic liver
- Track along the intrahepatic portal tract system to create a treelike tumorous mass within a portion of the liver.





# Microscopic finding of CCA

- Typically are mucinous- producing adenocarcinomas
- Most are well to moderately differentiated
- Abundant fibrous stroma (desmoplastic stroma)
- Common lymphovascular & perineural invasion
  - ✓ Extensive extrahepatic & intrahepatic metastasis





# CCA – Clinical Picture & Prognosis

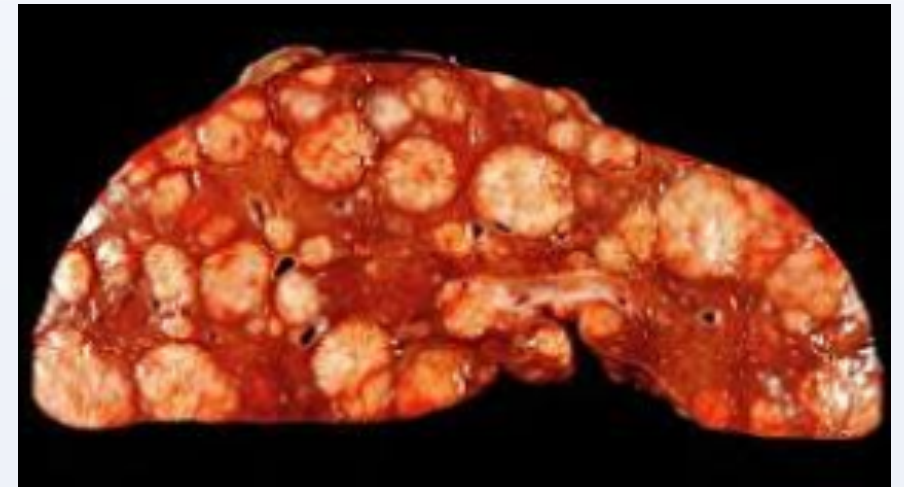
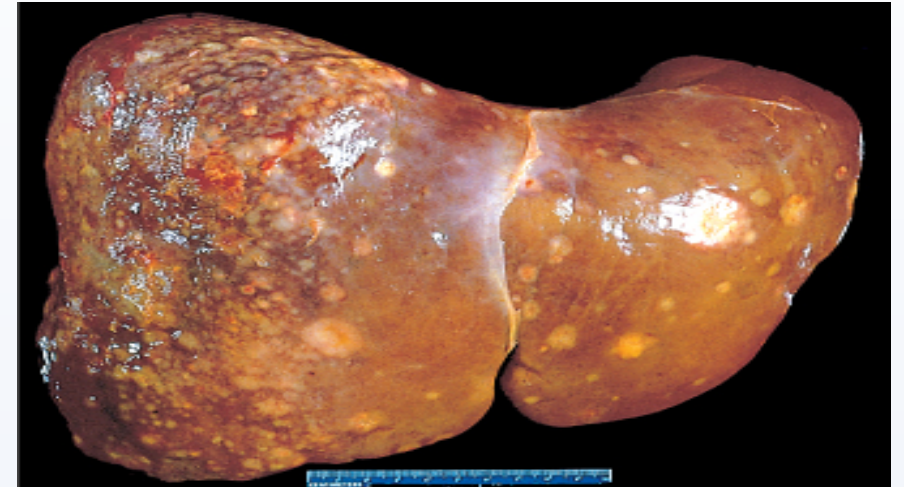
- Intrahepatic CCAs are not usually detected until late in their course and come to the attention because of obstruction of bile flow, or as a symptomatic liver mass
- Hilar and distal tumors present with symptoms of biliary obstruction, cholangitis, and right upper quadrant pain
- Prognosis is poor 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-fetoprotein is not elevated

# Metastatic tumors

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# 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

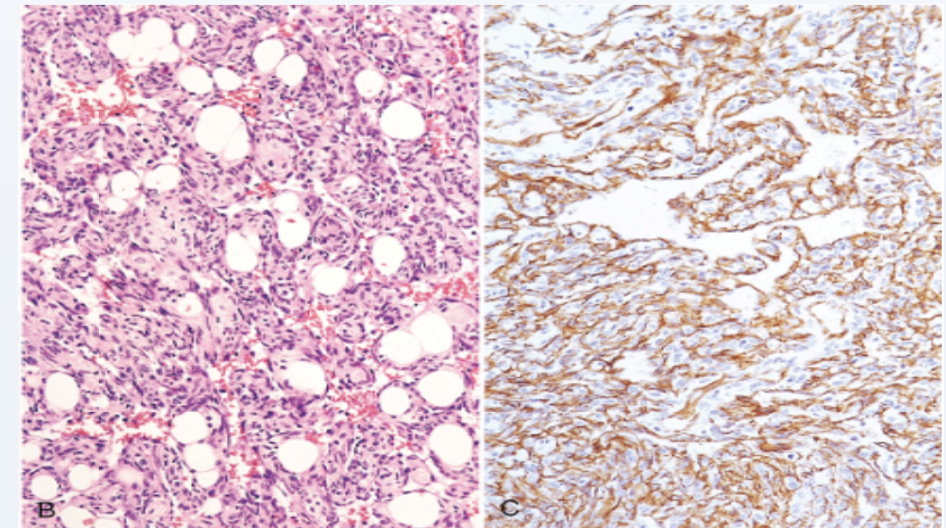
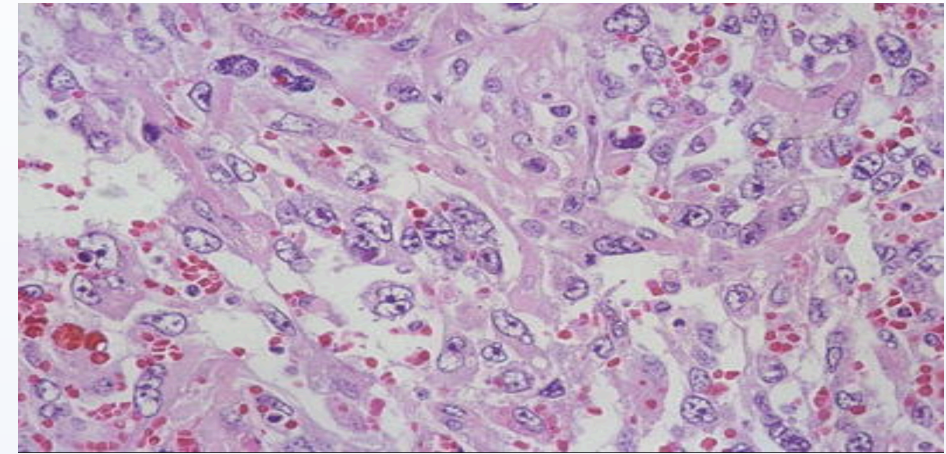


# Other Malignant tumors

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# Angiosarcoma

- Pleomorphic endothelial cells with large hyperchromatic nuclei, giant cells in frequent mitosis and irregular anastomosing vascular channels. The cells may appear spindle shaped
- Cirrhosis is present in 20% to 40% of the cases
- These have also been linked to vinyl chloride and thorotrast exposure



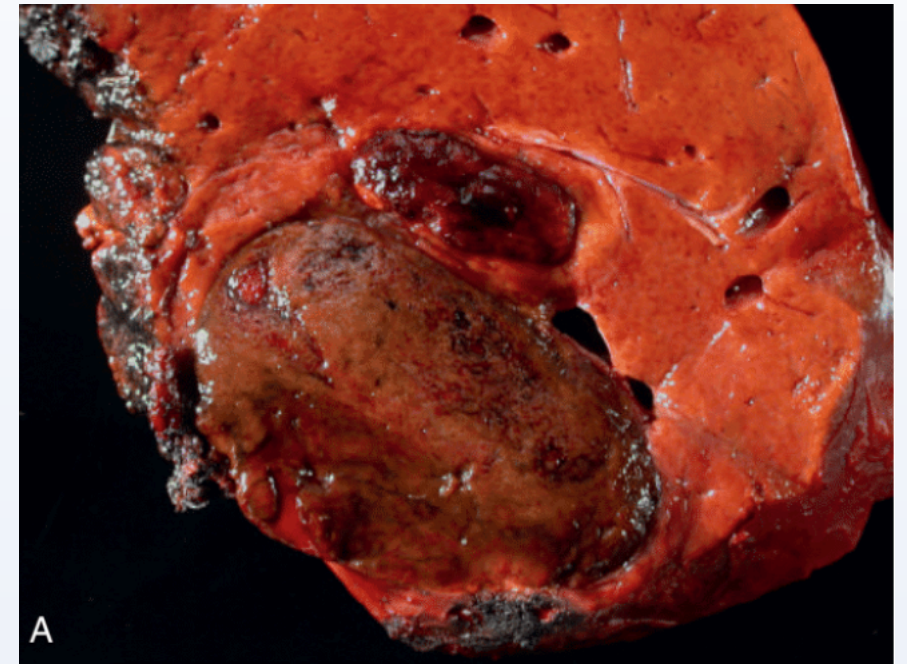
# **Benign Hepatic Tumors**

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# Hepatocellular Adenomas

- Benign neoplasms developing from hepatocytes
- 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 intraabdominal bleeding



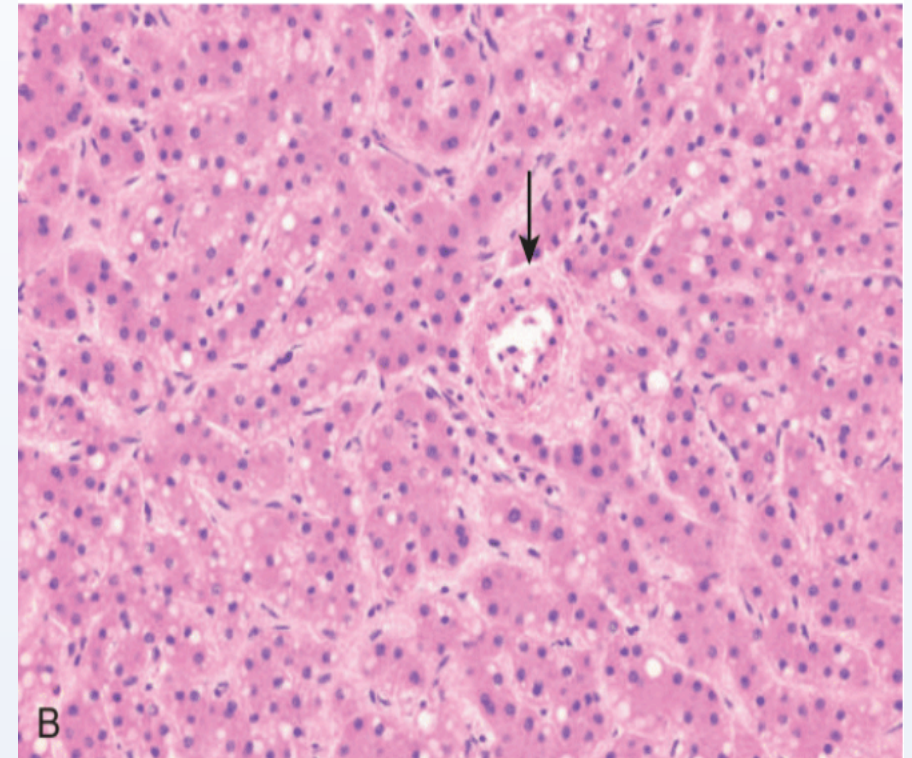
# Hepatocellular Adenomas

- **Molecular Subclassification:**

1. Low risk for malignant transformation
2. Intermediate risk for malignant transformation
3. High risk for malignant transformation

- **Microscopic:**

1. Cords of hepatocytes, with an arterial vascular supply (arrow) and no portal tracts





## 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.
  - The 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 Carcinoma**

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# Pancreatic Carcinoma

- **Epidemiology**

1. 80% in persons 60-80 years of age
2. It is more common in blacks than in whites
3. Males more than females
4. Fourth leading cause of cancer deaths in the United States, preceded only by lung, colon, and breast cancers
5. Highest mortality rates of any cancer

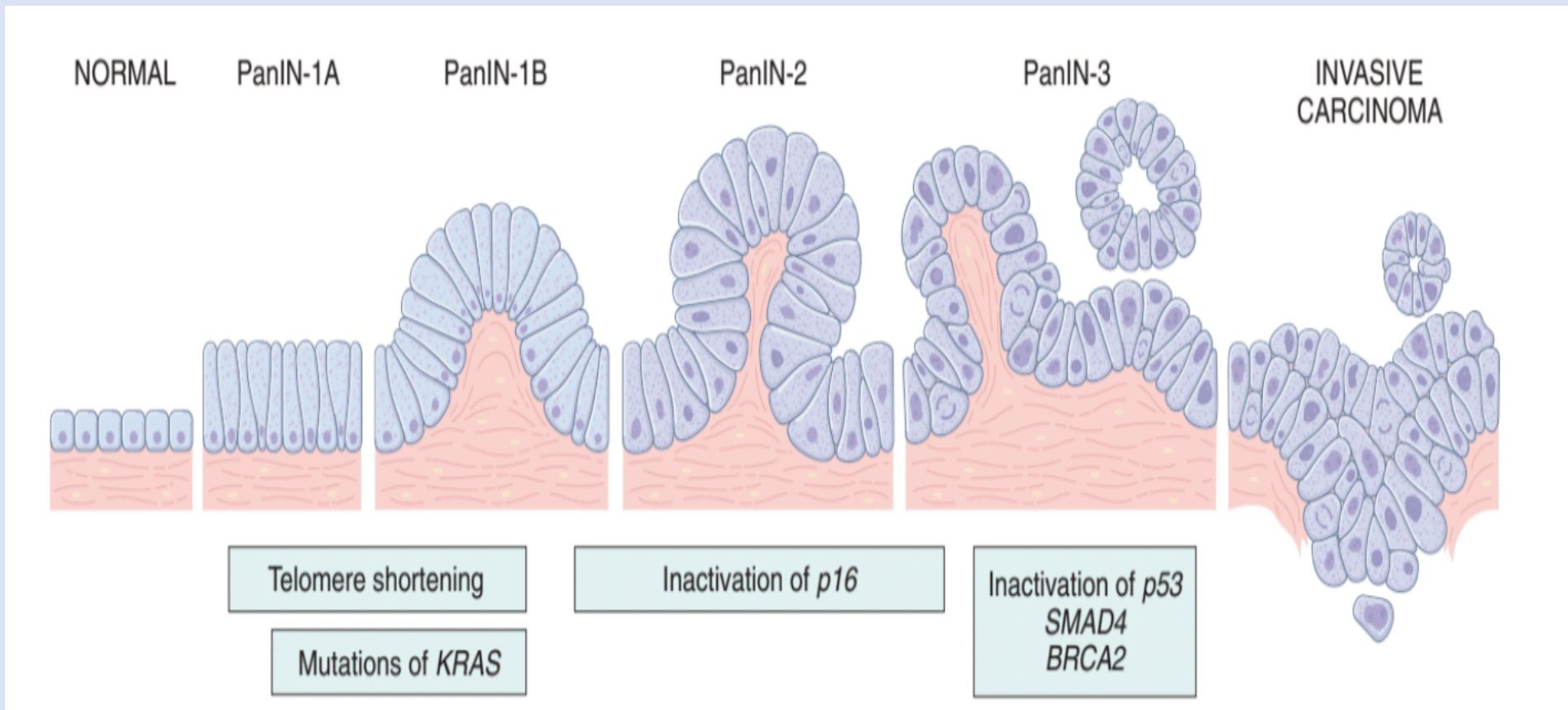
# Pancreatic Carcinoma

## Etiology:

1. The strongest environmental influence is smoking
2. Long-standing chronic pancreatitis and DM
3. Familial clustering, e.g. germline mutation of familial breast/ovarian cancer gene BRCA2 are seen in 10% of cases

# Pathogenesis

Arises from precursor lesions (PanINs) as result of progressive accumulation of inherited & acquired genetic mutations in pancreatic epithelium

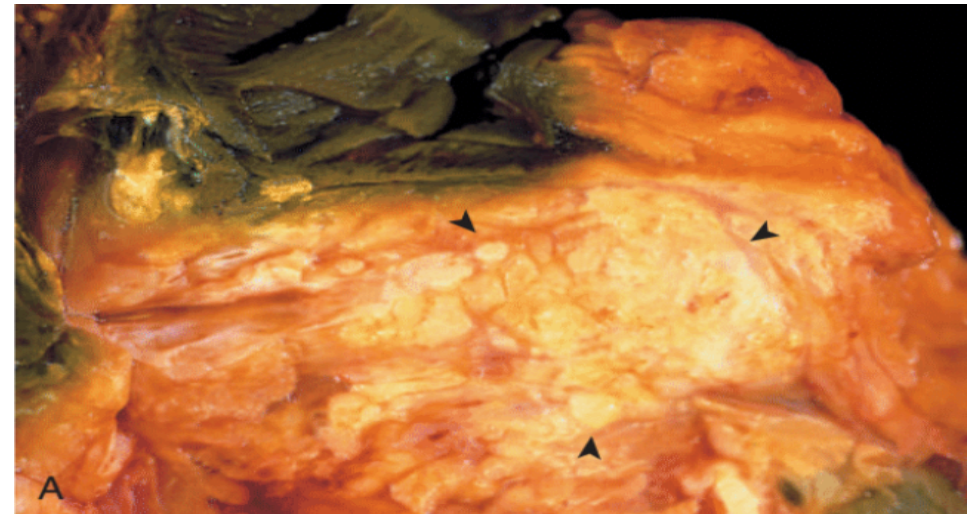
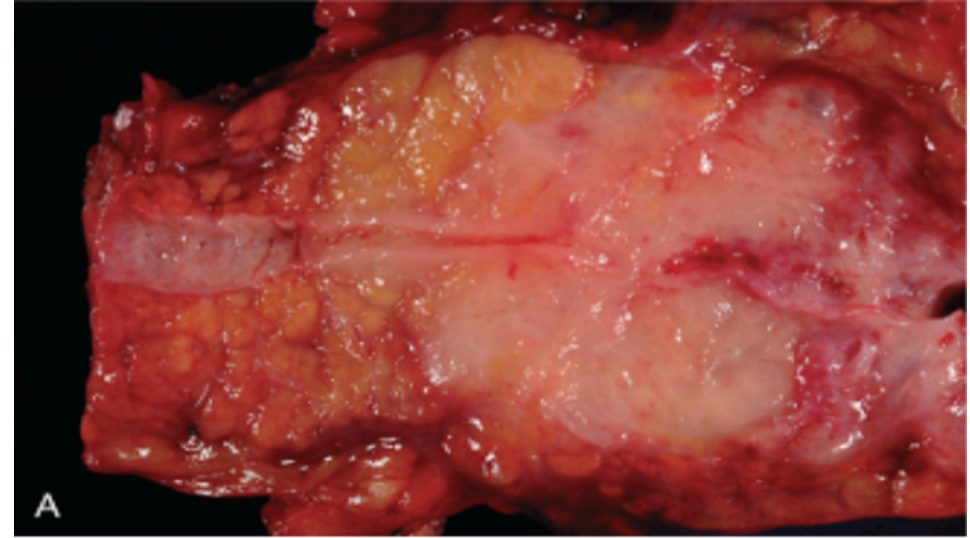


Four genes are most affected by somatic mutations in this neoplasm: *KRAS*, *CDKN2A/p16*, *SMAD4*, and *TP53*



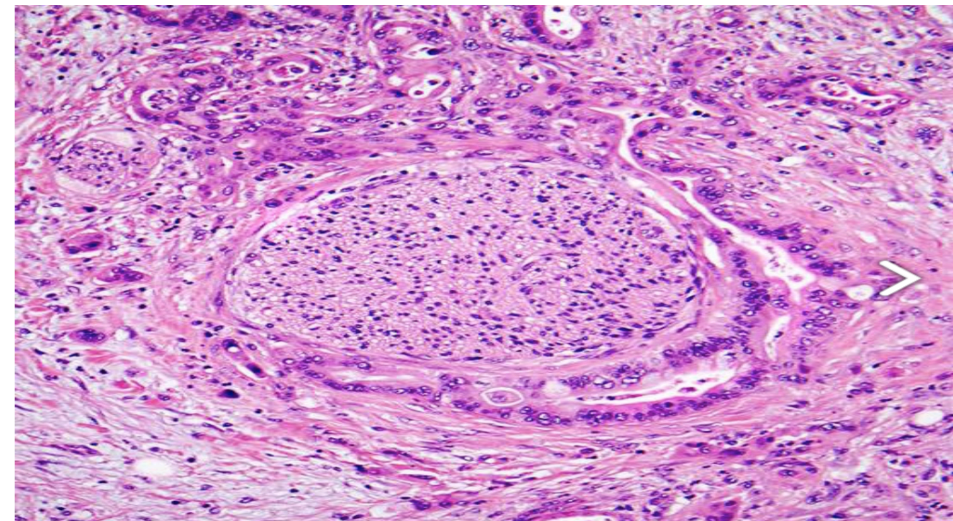
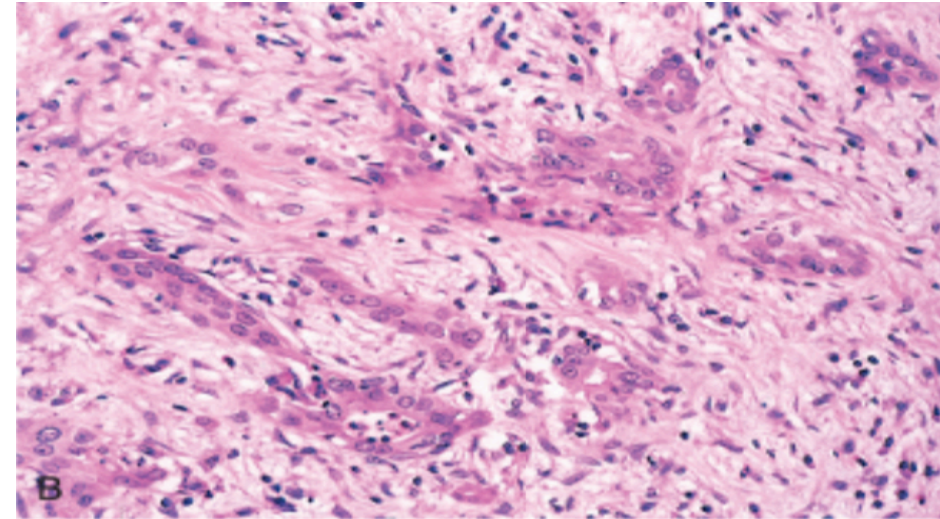
# Pancreatic Carcinoma - Gross finding

- 60% arise in the head of the gland
- 15% in the body
- 5% in the tail
  
- Hard, gray-white, stellate, poorly defined masses



# Pancreatic Carcinoma - Microscopic finding

- 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

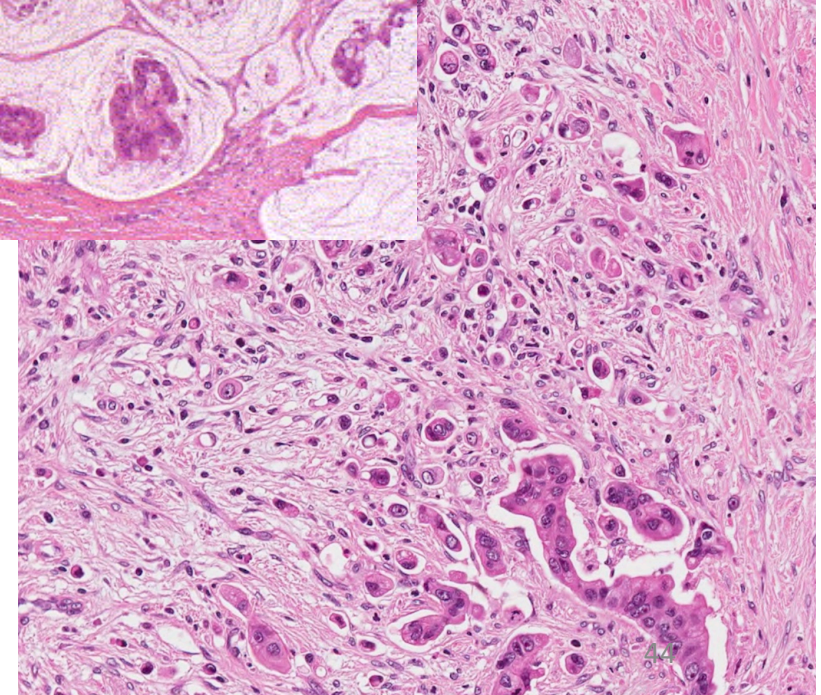
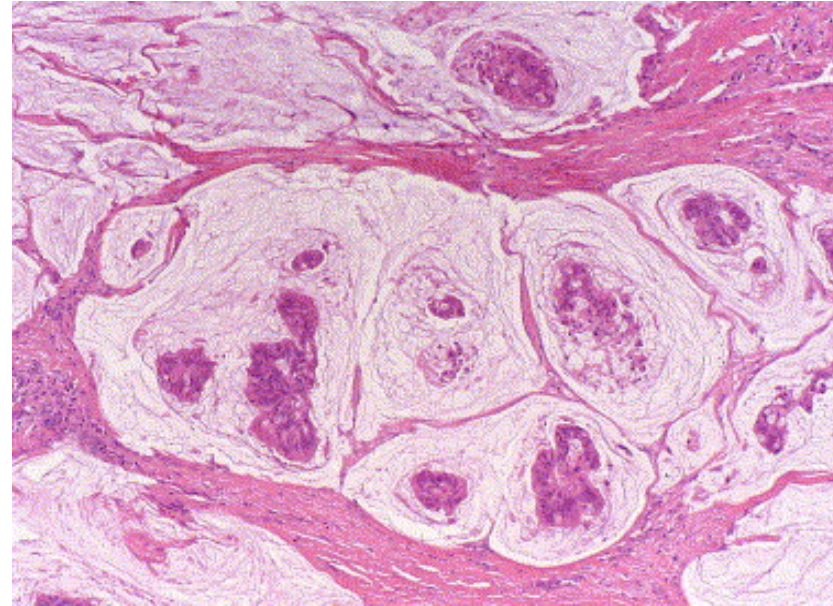




# Pancreatic Carcinoma - Microscopic finding

Less common variants 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



# Pancreatic Carcinoma - Clinical Picture

- Remain silent until they invade into adjacent structures.
- Erode the nerve fibers in retroperitoneum lead to pain (1<sup>st</sup> symptom)
- Tumors of the head of pancreas leads obstructive jaundice
- Jaundice Wt. loss, anorexia, generalized malaise & weakness are signs of advanced disease
- Migratory thrombophlebitis (Trousseau sign,) occurs in about 10% of patients due to platelet-aggregating factors and procoagulants from the carcinoma or its necrotic products

# Pancreatic Carcinoma - Prognosis

- 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%**





## SUMMARY

### PANCREATIC NEOPLASMS

- 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.

**Thank you for your attention**

**References:**

- **ROBBINS BASIC PATHOLOGY,  
TENTH EDITION**

