



# Cancers of Liver and Pancreas

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## Lecture 12

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### Characteristics:

- The **liver** and **lungs** are the visceral organs that are most often involved by **metastatic tumors**.
- The most frequent organ to metastasis to the liver is **colon**.
- Primary carcinomas of the liver are relatively uncommon.

### Types:

- Most arise from hepatocytes and are termed **hepatocellular carcinoma** (HCC) (presence of  **$\alpha$ -fetoprotein in better differentiated cases**). Much less common are carcinomas of bile duct origin, **cholangiocarcinomas** (no  **$\alpha$ -fetoprotein**).
- There are two rare forms of primary liver cancer **hepatoblastomas** (seen in children) and **angiosarcomas** (sarcoma = mesenchymal cells or connective tissue).

### 1. Hepatocellular Carcinomas:

#### Incidence and epidemiology:

##### Male predominance

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

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.

#### Pathogenesis of HCC:

The following have been implicated in human hepatocarcinogenesis:

- Viral infection (HBV, HCV): extensive studies link chronic HBV and chronic HCV infection with liver cancer.
- Cirrhosis: the development of cirrhosis appears to be an important, but not requisite (**necessary**), contributor to the emergence of HCC.
- Chronic alcoholism.
- Food contaminants (primarily **aflatoxins** from **aspergillus**). High exposure to dietary aflatoxins derived from the fungus *Aspergillus flavus*. These highly carcinogenic toxins are found in "moldy" grains and peanuts (**usually it's seen in the Far East**).
- Other conditions include **tyrosinemia** (autosomal recessive defect in tyrosine metabolism resulting in liver and kidney disturbances and mental retardation.) and **hereditary hemochromatosis** (iron overload).



### Morphology of HCC:

Grossly it may be

1. **unifocal** mass.
2. **Multifocal**, multiple nodules of variable size.
3. **Diffusely infiltrative** cancer.

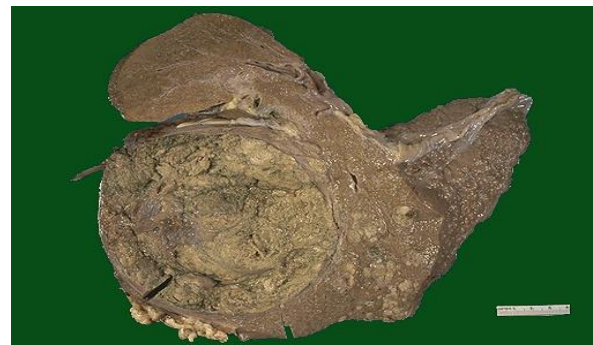
All three patterns may cause liver enlargement.

**All patterns of hepatocellular carcinomas have a strong tendency for invasion of vascular channels.**

- Extensive **intrahepatic** metastases may occur.
- 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.

- In well-differentiated and moderately well-differentiated tumors, cells that are recognizable as **hepatocytic in origin**. **Bile pigment is usually present**. The malignant cells **may be positive for alpha ( $\alpha$ )-fetoprotein**.
- In poorly differentiated forms, tumor cells can take on a **pleomorphic** appearance with numerous anaplastic giant cells, can become small and completely undifferentiated cells.
- The neoplasm is large and bulky and has a greenish cast because it contains bile. To the right of the main mass are small **satellite nodules**.



Another entity of a hepatocellular origin that has been put into another category is:

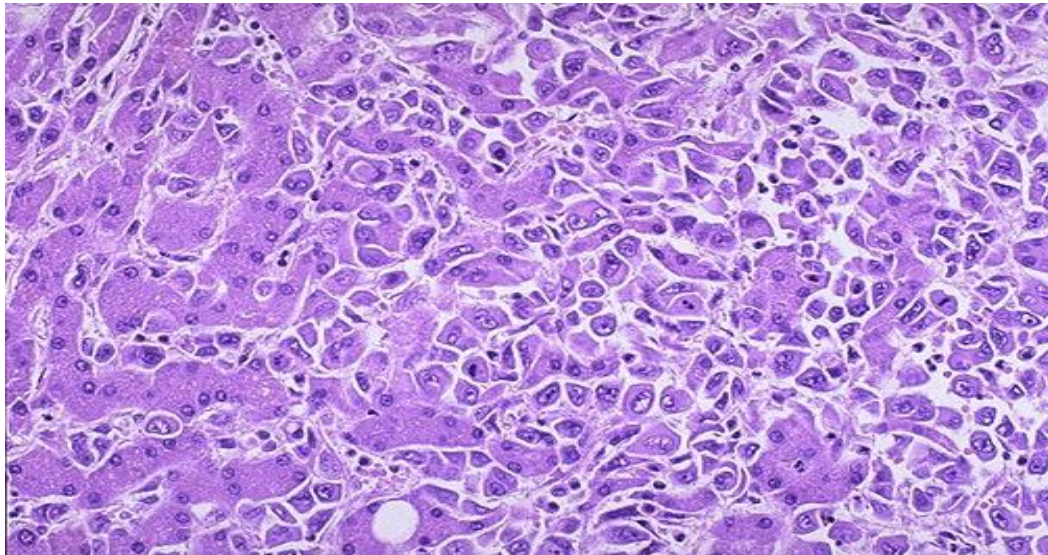
#### - **Fibrolamellar Carcinoma:**

A distinctive variant of hepatocellular carcinoma is the fibrolamellar carcinoma.

**Incidence:** occurs in **young male and female** adults (20 to 40 years of age), has **NO** association with HBV or cirrhosis, and often has a **better prognosis**.

**Morphology:** it usually presents as single large, hard "scirrhous" tumor with **fibrous bands** coursing through it.

**Microscopically:** it is composed of **well-differentiated** polygonal cells growing in nests or cords and separated by parallel lamellae of dense collagen bundles.



### 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.

This protein lacks specificity, where it can be elevated in a number of different diseases especially liver diseases and necrosis. Very high levels are almost only seen with HCC.

We can detect  **$\alpha$ -fetoprotein** on biopsy using **immunohistochemistry** (antigen/antibody reaction + chromogen).

### Complications:

Overall, death usually occurs from:

1. Cachexia (or **wasting syndrome** is loss of weight, muscle atrophy, fatigue, weakness, and significant loss of appetite).
2. Gastrointestinal or esophageal variceal bleeding. **complications of the portal hypertension.**
3. Liver failure with hepatic coma.
4. Rupture of the tumor with fatal hemorrhage.

## 2. Cholangiocarcinoma:

**Definition:** it is a malignancy (**Adenocarcinoma**) of the **biliary tree**, arising from bile ducts within and outside of the liver.

### The risk factors:

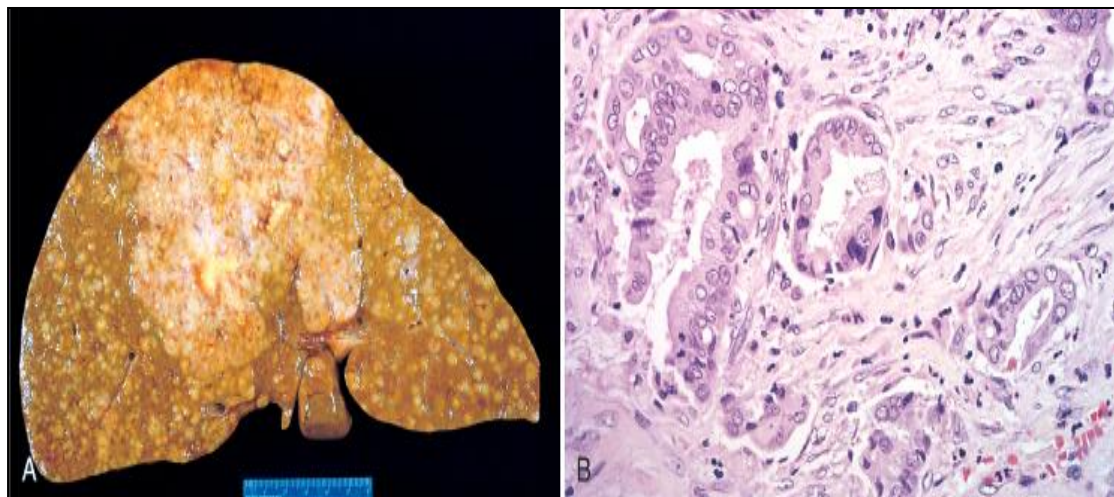
- Primary sclerosing cholangitis,
- Congenital fibropolycystic diseases of the biliary system (particularly Caroli disease (Congenital cystic dilatation of the intrahepatic bile ducts) and choledochal cysts (congenital conditions involving cystic dilatation of bile ducts.))
- Previous exposure to Thorotrast (formerly used in radiography of the biliary tract).
- In the Orient (The countries of Asia, esp. eastern Asia), the incidence rates are higher, and it is due to chronic infection of the biliary tract by the liver fluke *Opisthorchis sinensis* (the Chinese liver fluke, is a human liver worm).

### Morphology:

**Intrahepatic cholangiocarcinomas** occur in the non-cirrhotic liver and may track along the intrahepatic portal tract system to create a treelike tumorous mass within the liver or a massive tumor nodule. Lymphatic and vascular invasion are common.

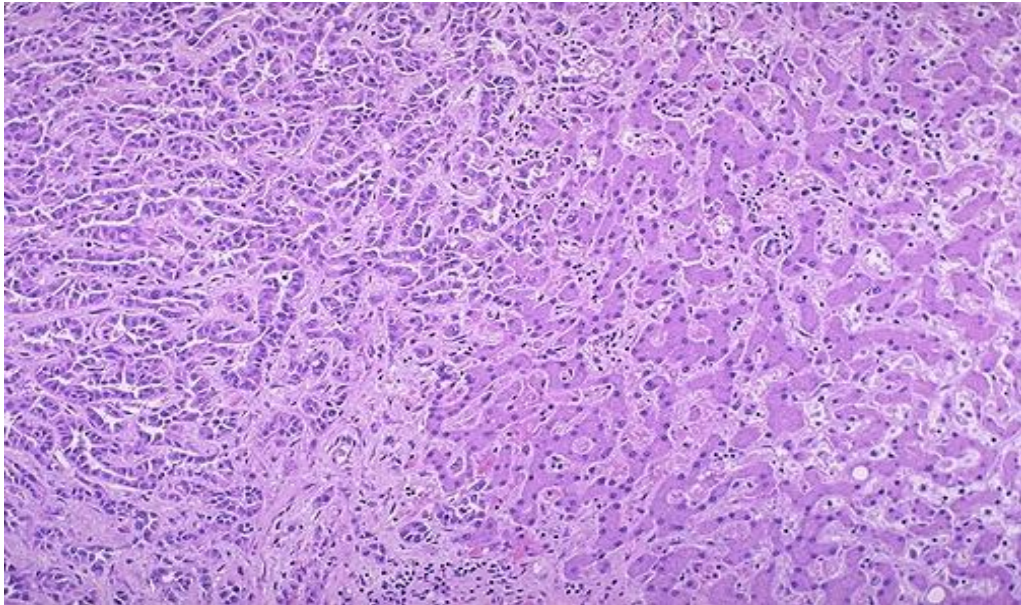
**By microscopy:** it resembles adenocarcinomas arising in other parts of the body. Most are well to moderately differentiate. **Cholangiocarcinomas are rarely bile stained**, because differentiated bile duct epithelium does not synthesize bile.

- **Mixed** variants occur, in which elements of both hepatocellular carcinoma and cholangiocarcinoma are present.
- Hematogenous metastases to the lungs, bones (mainly vertebrae), adrenals, brain. Lymph node metastases to the regional lymph nodes are also found



The carcinoma at the left has a glandular appearance. Cholangiocarcinomas do not make bile, but the cells do make mucin, and they can be almost impossible to distinguish from metastatic **adenocarcinoma** on biopsy or fine needle aspirate.





### Clinical Features:

- Intrahepatic cholangiocarcinoma is usually detected late in its course, either as the result of obstruction to bile flow through the hilum of the liver or as a symptomatic liver mass.

### Laboratory findings:

Alpha-fetoprotein is **NOT** elevated.

**Treatment:** aggressive surgery remains the only treatment offering hope for long-term survival.

**Prognosis:** is poor **because of the late discovery and the anatomical location**. The median time from diagnosis to death is 6 months.

### 3. Metastatic Tumors:

Metastatic involvement of the liver is far **more common** than primary neoplasia.

**Causes:** the most common primaries producing hepatic metastases are those of the **breast, lung, and colon**, however, any cancer in any site of the body may spread to the liver, including **leukemias** (is a type of cancer of the blood or bone marrow) and **lymphomas**.

### Morphology:

- Typically, 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.
- Numerous mass lesions of variable size. Some of the larger ones demonstrate central necrosis. The masses are metastases to the liver.



#### 4. Angiosarcoma:

##### Microscopically:

This consists of pleomorphic endothelial cells with large hyperchromatic nuclei, **giant cells** (the malignant cells have multiple nuclei) in frequent mitosis and irregular anastomosing vascular channels. The cells may appear spindle shaped and cirrhosis is present in 20% to 40% of the cases.

**Cause:** These have also been linked to vinyl chloride and thorostrast exposure.

**Laboratory test:** immunohistochemistry.

#### Malignant tumors of the pancreas:

##### Pancreatic Carcinoma:

**Definition:** it is carcinoma of the **exocrine pancreas**. It arises from **ductal epithelial** cells.

##### Incidence:

It occurs in the **6<sup>th</sup> to 8<sup>th</sup> decade**, blacks more than whites, males more than females, diabetics more than non-diabetics, and **obese patient more than non- obese**.

##### Morphology:

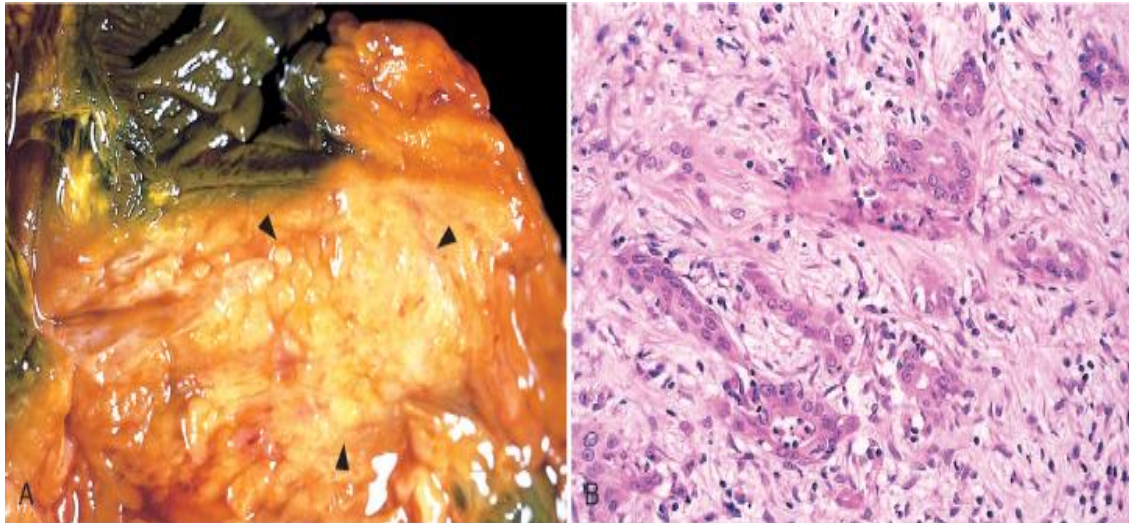
- Approximately 60% of cancers of the pancreas arise in the **head** of the gland, 15% in the body, and 5% in the tail; in 20%, the neoplasm diffusely involves the entire gland.
- Carcinomas of the pancreas are usually hard, stellate (**star-like**), gray-white, poorly defined masses.
- Majority of carcinomas are ductal adenocarcinomas. Two features are characteristic: It is highly invasive, and it elicits an intense non-neoplastic host reaction called a "**desmoplastic response**" (**fibroblastic proliferation secondary to the infiltrating cancer composed of fibroblasts, lymphocytes, and extracellular matrix**).
- Peripancreatic, gastric, mesenteric, omental, and portahepatic lymph nodes are frequently involved. Distant metastases occur, principally to the lungs and bones.
- Less common variants of pancreatic cancer include **acinar cell carcinomas**, **adenosquamous carcinomas**, and **undifferentiated carcinomas with osteoclast-like giant cells**.

##### Clinical Features:

1. Jaundice **by obstructing the common biliary duct with enlargement of the head of the pancreas**.
2. Weight loss.
3. excruciating **pain (because pancreas is a retroperitoneal organ that lies next to nerves and it's usually the first symptom)**,
4. Massive metastasis to liver

5. **Migratory thrombophlebitis** (This is a result of elaboration of platelet aggregating factors and procoagulants from the tumor or its necrotic products, seen in old age)

**Prognosis:** pancreatic cancer has one of the **highest mortality** rates of any cancer. Nearly all patients with pancreatic die, with a 5-year survival rate of less than 5%.



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A cross-section through the head of the pancreas and adjacent common bile duct showing:  
A) Both an ill-defined mass (arrowheads) and green discoloration of the duct resulting from total obstruction of bile flow.  
B, Poorly formed glands are present in a densely fibrotic (desmoplastic) stroma