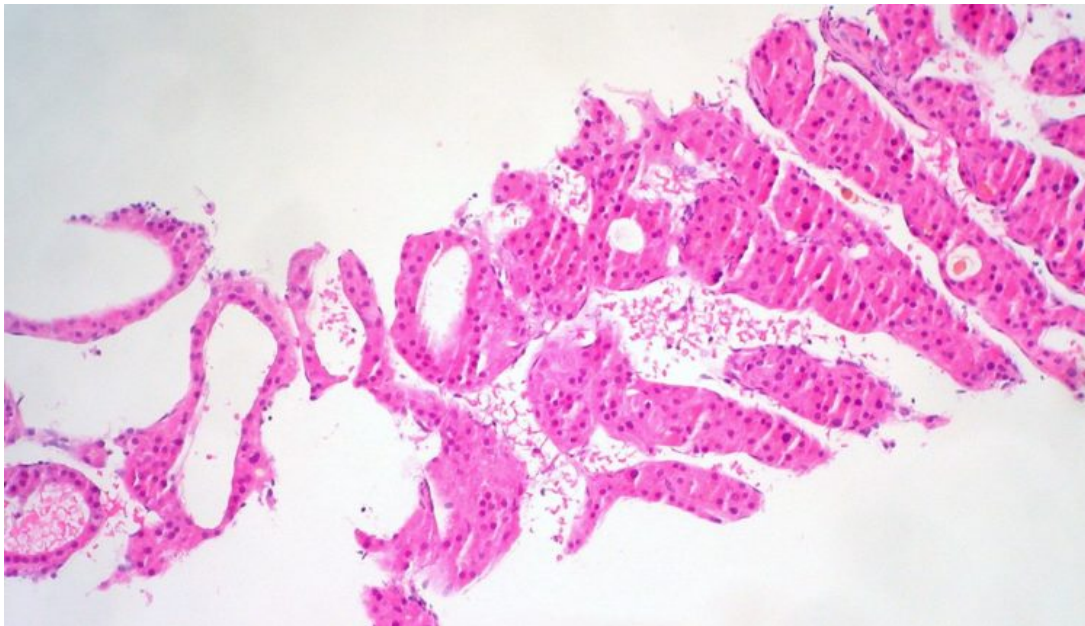


Space-Occupying Lesions in the Liver

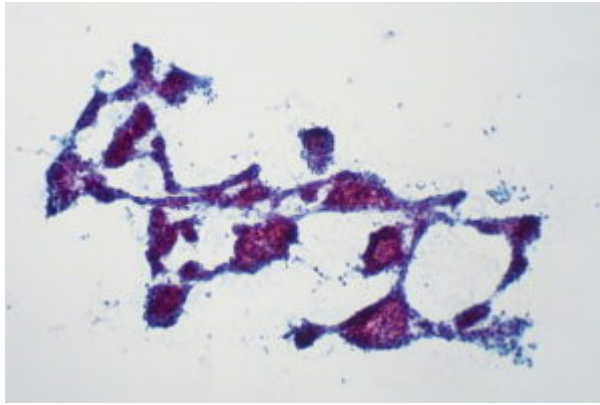
[See online here](#)

The significant prevalence of mass lesions in the liver among the general population has prompted the emphasis on understanding each of the condition's clinical presentation, diagnosis, and treatment. The lesions usually represent abdominal pain or abnormal abdominal physical findings like distension or palpable abdominal mass. Another reason to fully understand the characteristics of the different space-occupying lesions in the liver is the fact that the treatment varies depending on the type of lesion found in the liver. Here, we briefly discuss the epidemiology and features of the different space-occupying lesions in the liver.



Primary Malignant Tumors

Hepatocellular carcinoma



[Image](#): "Hepatocellular carcinoma, pathological and histological images courtesy of Ed Uthman at flickr." by Ed Uthman from Houston, TX, USA, uploaded by CFCF, License: [CC BY 2.0](#)

Hepatocellular carcinoma occurs mostly in patients having chronic liver disease and cirrhosis.

Epidemiology

Among all cancer patients all over the world, hepatocellular carcinoma makes up about 5.4% of the overall incidence. It is very prominent among those who have had **hepatitis B** infection.

Locations with the most cases of hepatocellular carcinoma include **Asian and sub-Saharan African countries which are known as endemic areas of hepatitis B and hepatitis C**. However, with the increasing rate of **hepatitis C** infections, western countries such as the United States are contributing more and more cases to the total prevalence of hepatocellular carcinoma in the recent years.

Another risk factor that could contribute to the development of hepatocellular carcinoma is the **exposure to aflatoxin** which is very common in the aforementioned countries with prevalent hepatitis B infections.

Pathogenesis

Although the occurrence of hepatocellular carcinoma is associated with the existence of **cirrhosis** in the liver, cirrhosis in itself does not trigger the pathogenesis of the condition. Instead, the two conditions occur in a parallel fashion in a span of years. The inflammatory changes marked in cirrhosis of the liver along with necrosis and fibrosis can induce hepatocellular carcinoma.

What predisposes people into having hepatocellular carcinoma is infection with either hepatitis B or C. As mentioned, another risk factor for this condition is the chronic exposure to **alcohol and aflatoxin**, a toxin produced by *Aspergillus* which contaminates staple food items. The ability of aflatoxin to contribute to hepatocellular carcinoma development is improved when there is a coexisting hepatitis B or C infection as well.

Morphology

The **cellular dysplasias** involved in hepatocellular carcinoma include **hepatocellular adenoma** (will be discussed separately), **large cell change, small cell change, low-dysplastic nodules**, and **high-grade dysplastic nodules**. These precursor lesions are described as following:

Large cell change - cells near the septa or the portal tracts are most commonly

affected; appear larger than normal hepatocytes with many large and moderately pleomorphic nuclei; with the normal nuclear-cytoplasmic ratio

Small cell change – with mild nuclear hyperchromasia and pleomorphism; this change usually results in the formation of small expansile nodules in a single lobule in the liver parenchyma

Low-grade dysplastic nodules – clonal nodules that do not have cytologic or architectural atypia and have the possibility of being neoplastic. Blood supply is still a combination of hepatic arterial and portal venous blood.

High-grade dysplastic nodules – include significant cytologic and architectural features such as pseudoglands, trabecular thickening, and small cell changes that are suggestive of hepatocellular carcinoma. However, these characteristics are not enough to come up with a definitive diagnosis of hepatocellular carcinoma.

Grossly, hepatocellular carcinoma may appear either as a large unifocal mass, as multifocal nodules with varying sizes, or as diffuse infiltrations in the entire liver. Intrahepatic metastasis is common when tumors become 3 cm in size.

Clinical features

Since it usually occurs with **cirrhosis** and **chronic hepatic viral infection** in predisposed individuals, the manifestations of hepatocellular carcinoma may be masked with other general signs and symptoms before being significantly apparent. Nonspecific manifestations include abdominal pain, malaise, fatigue, weight loss, hepatomegaly, and abdominal fullness.

Diagnosis

Although not very definitive when it comes to diagnosis, laboratory exams may help in reinforcing the characterization of the lesion. Elevated **serum α -fetoprotein** may be expected in about half of the cases. Imaging studies such as **ultrasonography**, **computed tomography**, and **magnetic resonance imaging** may help visualize the outlines and other features of the lesion. These may even help in describing the degree of **arterialization** of the [tumors](#).

Prognosis

With its increasing size, a hepatocellular carcinoma gradually disturbs normal hepatic function and can **metastasize** to other locations such as the [lungs](#). The cause of death for patients with hepatocellular carcinoma may be cachexia, gastrointestinal variceal bleeding, liver failure with hepatic coma and hemorrhage due to tumor rupture.

Treatment

Transcatheter arterial chemoembolization (**TACE**), low dose brachytherapy, chemotherapy are opted to manage the patient. Surgical intervention is recommended in case of the insensitivity of the patient towards chemotherapy and radiotherapy, resection of the tumor by partial hepatectomy is considered.

Intrahepatic cholangiocarcinoma

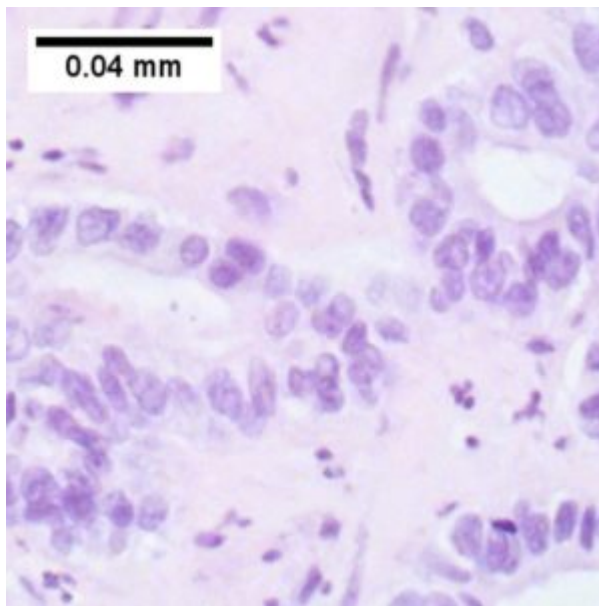


Image: "Cholangiocarcinoma, intrahepatic, large duct type." by TexasPathologistMSW - Own work, License: [CC BY-SA 4.0](https://creativecommons.org/licenses/by-sa/4.0/)

Cholangiocarcinoma is the malignancy that arises from the bile ducts and end at the ampulla of Vater. Intrahepatic tumors are less common.

Epidemiology

Cholangiocarcinoma, in general, is the 2nd most common primary malignancy in the liver. It arises from the epithelium lining the biliary duct and can either be **extra- or intrahepatic**. The latter comprises about a fifth of all the cases of liver cancer.

Since the occurrences of risk factors for the disease vary from one population to another, the distribution varies widely from one place to another. **Chronic fluke infection** which is especially endemic in certain Asian regions contributes to the development of the disease. It affects mostly males and females of age 60 and 70 years.

Pathogenesis

It usually starts with a **chronic bout of inflammation or cholestasis**. In the presence of genetic predisposition, mutations in certain oncogenes and other genes that encode bile salt transporters trigger the pathogenesis of cholangiocarcinoma. [Mutations](#) in the following genes may be implicated in the disease process:

- **K-ras gene**
- **TP53**
- **P16**

The tumors grow slowly, to infiltrate into the walls of the biliary duct and may extend to liver portal vasculature and regional lymph nodes and pancreatic duodenal chains.

Clinical features

Manifestations of intrahepatic cholangiocarcinoma are somewhat similar to and more prominent than that of hepatocellular carcinoma. **Progressive jaundice, weakness,** and **weight loss** may become apparent in advanced stages.

Morphology

Cholangiocarcinomas are usually **mucus-producing adenocarcinomas**. They can either

be well to moderately differentiated and have a **well-delineated glandular/tubular structures** that are outlined by malignant cells.

Treatment

Treatment of Cholangiocarcinomas involves stenting, photodynamic therapy, radiation therapy, chemotherapy followed by complete surgical resection to facilitate a complete cure.

Hepatoblastoma

Epidemiology

This tumor is very common among young children younger than 3 years.

Pathogenesis

Hepatoblastomas are described as having a **constantly activated WNT and β -catenin signaling pathways**, and **APC gene** mutations. This disorder can occur in patients with **familial adenomatous polyposis**. Mutations in the TGF- β pathway regulating gene, the **FOXP1** may also be implicated.

Morphology

There are 2 variants known:

- **Epithelial type** - polygonal cells that form acini, tubules or papillary structures
- **Mixed epithelial and mesenchymal type** - contains areas with mesenchymal differentiation that could include primitive mesenchyme, osteoid, cartilage or muscular cells.

Clinical features

- Anorexia
- Vomiting
- Nausea
- Abdominal pain
- Itchy skin
- Weight loss

The only treatment available is the surgical removal of the tumor.

Hemangiosarcoma

Epidemiology

It is the most common mesenchymal neoplasm in the liver, despite its overall rare occurrence.

Pathogenesis

The most commonly known implicated cause for the pathogenesis of hemangiosarcoma is exposure to **thorium dioxide**. Exposure to insecticides and ingestion of liquors contaminated with **arsenic** is also a significant risk factor. Previous psoriasis treatments containing **potassium arsenite** have been found to cause hemangiosarcoma as well. Workers that are exposed to **vinyl chloride monomer** are also at risk of developing the

lesion.

Metabolites from the known substances are found to be highly reactive and able to form DNA adducts and G to A transitions in the **K-ras** and **TP53 genes**.

Morphology

Hemangiosarcomas are known for their **blood-filled cysts**. Although not contained in a capsule, they are well circumscribed and can bulge beneath the capsule lining the entire liver.

Precursor lesions include the enlargement of the cells lining the sinusoids with hyperchromatic nuclei in poorly defined loci in the entirety of the liver. Soon enough, the rapidly developing lesions become supported by collagen, hence their well-defined borders.

Other primary malignant tumors of the liver

Other rare tumors in the liver that could progress to cancerous growths include:

- Epithelioid hemangioendothelioma
- Undifferentiated sarcoma
- Liposarcoma
- Lymphoma
- Rhabdomyosarcoma

Hepatic Metastases

The double blood supply of the [liver](#) puts it in a high risk for metastasis from growths arising on other locations of the body. The porous nature of the sinusoids also allows for the easy penetration of malignant cells into the liver tissue.

[Metastasis](#) in the liver commonly arises from growths found in the [stomach](#), pancreas, colon, lungs, and [breasts](#). Most of the time, symptoms hide behind those manifested by the primary tumors. Signs and symptoms usually include malaise, abdominal pain, weight loss, hepatomegaly, and jaundice.

Benign Tumors

Hepatocellular adenoma

Epidemiology and pathogenesis

It has been found out that hepatocellular adenomas are common among women who have taken **oral contraceptive steroids** for a long period of time. Its rarity among men and women who are not exposed to contraceptive steroids suggest a strong relationship. However, **heredity** still plays a large component in the development of the lesion.

Mutations in the **TCF1 gene** which encode for the **hepatocyte nuclear factor 1 α (HNF-1 α)** and alterations in the **WNT pathway** have been implicated in the pathogenesis of hepatocellular adenoma. In the latter, **β -catenin activation** has put many of the patients at risk for malignant development of the lesions. Finally, they can also be a result of **chronic inflammatory processes**.

Morphology

The morphology of hepatocellular adenomas varies depending on the type of genetic alterations present in the lesion:

- **HNF-1 α mutations** – fatty lesions; no cellular or architectural atypia
- **B-catenin mutations** – highly dysplastic architecture; with nuclear translocation indicating the active state
- **Inflammation** – contain fibrotic stroma, mononuclear inflammation, ductular reactions, dilated sinusoids, and telangiectatic vessels; produce excess amounts of C-reactive protein and serum amyloid A.

Prognosis

Pregnancy-associated with hepatocarcinoma has the risk of rupture of the adenoma leading to a high mortality rate of mother and the infant.

Cavernous hemangioma

Characterized as **mesenchymal blood vessel tumors in the liver**, these lesions are known to be the most common among the benign liver tumors. These **discrete red-blue nodules** that have a soft consistency are generally found beneath the **Glisson's capsule**. They are composed of vascular channels embedded in fibrous connective tissue. These lesions are commonly mistaken as metastatic lesions.

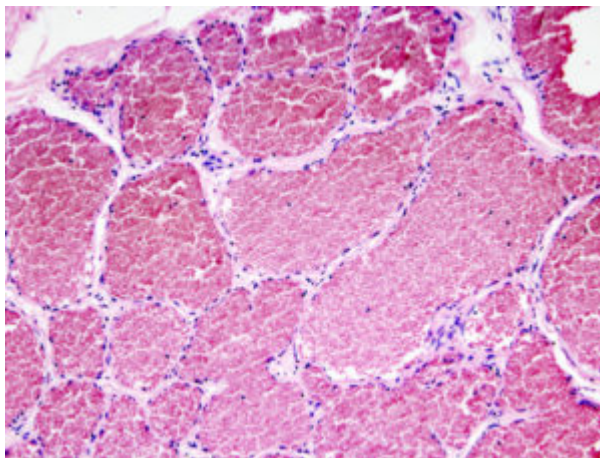


Image: "Histopathological image representing a cavernous hemangioma of the liver. Surgical excision of the lesion for the impending risk for rupture. Hematoxylin and eosin stain." by user: KGH - Own work, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

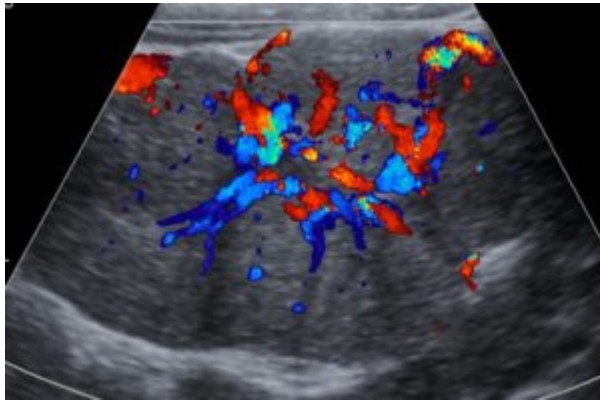
Other benign tumors of the liver

Rare benign tumors of the liver include:

- Infantile hemangioendothelioma
- Angiomyolipoma
- Bile duct adenoma
- Biliary cystadenoma
- Biliary adenofibroma

Tumor-Like Hepatic Lesions

Focal nodular hyperplasia



[Image](#): "Ultrasound image of malformed vessels within the fibrous scar of focal nodular hyperplasia." by © Nevit Dilmen, License: [CC BY-SA 3.0](#)

Epidemiology and pathogenesis

These solitary lesions are made up of hyperplastic cells that surround a central stellate scar in thickened plate pattern. They appear to be more common than hepatocellular adenoma and are frequently seen among women in the 3rd or 4th decade of their lives.

Although the cause of the lesions is yet to be found, it has been found out that alterations in the arteries of the small and medium-sized portal tracts suggest a part in the development of the lesions. They commonly occur with other vascular lesions. Others theorize that the development of the lesions may be hormone-dependent.

Morphology

Focal nodular hyperplasia appears as a firm light brown to yellowish mass in different sizes. It has a **dense central stellate scar** which divides the nodule into many parts with its radiating septa. These solitary nodules may be found beneath the **Glisson's capsule**.

When viewed under the microscope, the lesions resemble a focal form of inactive cirrhosis. Although the cells have not much difference to normal hepatocytes, they do not have the normal cord arrangement in relation to the other structures in a hepatic lobule.

Other tumor-like hepatic lesions

Other nodular disorders in the liver include:

- Nodular regenerative hyperplasia
- Macrogenic nodules
- Inflammatory pseudotumor

Hepatic Cysts

Fluid-filled sacs found in the liver are generally categorized into 3 types: **fibrocystic lesions; cystadenomas and cystadenocarcinomas;** and **hydatid cysts**. The cystic

conditions categorized under the fibrocystic diseases of the liver are the following:

- Simple Hepatic Cysts
- Polycystic Liver Disease
- Fibrocystic Disease Associated with Autosomal Recessive Polycystic Kidney Disease
- Von Meyenburg Complexes
- Caroli's Disease

Review Question

The correct answer can be found below the references.

A patient admitted due to nausea and vomiting, abdominal pain and severe weight loss are found to have intrahepatic lesions upon imaging studies. After finding out that the patient has had a history of intravenous drug use for 10 years in the past during the history taking, you perform additional tests (including a serum α -fetoprotein measurement), suspecting that the patient may have:

- A. Hepatocellular carcinoma
- B. Fatty lesions associated with HNF-1 α mutations in hepatocytes
- C. Angiomyolipoma
- D. Focal nodular cysts

References

Kumar V, Abbas AK and Aster JC. Robbins and Cotran pathologic basis of disease, 9th ed. Philadelphia, PA: Elsevier Saunders; 2015.

Feldman M, Friedman LS and Brandt LJ. Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management, 10th ed. Philadelphia, PA: Elsevier Saunders; 2016.

Correct answer: A

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Notes