Liver Cancer: Types of Hepatobiliary Tumors

Liver tumors are some of the more common neoplasms and are classified as either primary or secondary. Management varies depending on several factors such as type, size, and the spread of the cancer. Continue to read this article to learn key facts about the tumors of the liver including incidence, pathology, clinical features, diagnosis, and treatment.

Types of Hepatobiliary Tumors

Tumors of the liver can either be primary or secondary. Secondary tumors are the more common out of the two, however, primary tumors are not uncommon.

Primary hepatic neoplasms are ones that arise from liver cells and they are more commonly malignant. Secondary liver tumors are the metastases of malignant neoplasms from other parts of the body, especially the gastrointestinal tract, breast or the bronchus. And because they are metastases, they will usually present as multiple small liver lesions; primary neoplasms usually present as a single large lesion.
Benign Liver Tumors

Cavernous hemangiomas

Cavernous hemangiomas are the most common type of benign primary tumor of the liver. They are benign vascular tumors which occur within the blood vessels and can often be mistaken for metastatic tumors. These tumors are often **asymptomatic** and found **incidentally** during surgery, radiological examination (ultrasound, CT, MRI), or at autopsy. They appear as a red, spongy mass lying below the capsule of the liver.

Needle biopsy should **never** be done if a hepatic hemangioma is suspected because they have a very high risk of bleeding.

**Hepatic adenoma**

Hepatic adenomas are benign tumors that develop from hepatocytes. This is a rare tumor with an incidence of about 1 in 100,000. They are usually associated with females taking **oral contraceptive pills** and athletes abusing **anabolic steroids**. These tumors generally shrink when these drugs are stopped.

Hepatic adenomas are clinically significant because:

- They can commonly be mistaken for hepatocellular carcinomas.
- Adenomas subcapsular adenomas (under the liver capsule) tend to rupture, especially in high estrogen states like pregnancy. Rupture can result in life-threatening hemorrhage within the peritoneum.
- There is a small risk these tumors **can become malignant**.

**Pathophysiology**

Although there is a relationship between hormonal stimulation and the development of hepatic adenomas, the exact cause is not yet known. However, mutations in some genes involved in transcription factors HNF1 alpha and beta-catenin have been identified in a 50% and 15% of hepatic adenomas respectively.

**Clinical Presentation and Management**
Patients often present with a mass, a sudden onset right upper quadrant pain or with bleeding due to rupture of the liver capsule.

These tumors, even though benign, are usually resected due to the risk of malignant transformation.

**Focal nodular hyperplasia**

Focal nodular hyperplasia is not a true neoplasm. They hyperplastic mass lesions of the liver and are also associated with the use of oral contraceptive pills. These lesions are frequently solitary, subcapsular, well circumscribed, and rarely larger than 5 cm in size. On cut section, appearance is a gray-white central area with fibrous bands radiating to the periphery. These are benign lesions and **treatment is not recommended**.

**Malignant Liver Tumors**

Malignant tumors of the liver can be either be primary or secondary (metastatic).

Primary liver tumors are not common in the North America and Western Europe but are fairly common in other countries. About 20% to 40% of the cancers represent primary tumors of the liver.

Malignant tumors of the liver can arise from:

1. Hepatocytes – classified as **hepatocellular carcinoma**
2. Intrahepatic bile ducts – classified as **cholangiocarcinoma**
3. Mesenchymal structures such as the blood vessels – classified as **angiosarcoma** or **hemangioendothelioma**

**Hepatocellular carcinoma (HCC)**

**Incidence**

Hepatocellular carcinoma is the 5\textsuperscript{th} **most common cancer worldwide**. This cancer is also noted to be the 3\textsuperscript{rd} most frequent cause of cancer deaths. About 82% of the cases of hepatocellular carcinoma occurring in developing countries are associated with chronic hepatitis B virus (HBV) infections. The incidence of hepatocellular carcinoma is higher
among males with a ratio of 2.4:1.

**Etiology**

The exact cause of hepatocellular carcinoma is unknown but several risk factors have been identified. Four major risk factors associated with hepatocellular carcinoma are:

1. **Chronic viral infection (Hepatitis B and Hepatitis C virus infection)**

Carriers of Hepatitis B virus (HBV) infection are at an extremely high risk of developing hepatocellular carcinoma. In areas of increased incidence of Hepatitis B virus infection, 90% of the cases with Hepatocellular carcinoma are positive for HBV infection. Hepatocellular carcinoma is common in Africa and the far east countries and they have an increased rate of hepatitis carriers. This may be due to the vertical transmission of the virus from the mother to child. The risk of hepatocellular carcinoma in Hepatitis C virus infection (HCV) is higher than HBV infection.

2. **Chronic alcoholism**

More than 80% of the patients who develop hepatocellular carcinoma in developed countries of the Western world (where HBV is not prevalent) have cirrhosis of the liver.

3. **Non-Alcoholic Steatohepatitis (NASH)**

4. **Aflatoxins**

Aflatoxin is a toxic product of the fungus Aspergillus flavus which grows on peanuts and grains. Aflatoxins are toxic to liver cells as they can bind covalently to the cellular DNA and cause specific mutations. Chronic ingestion of aflatoxins may be partially responsible for the development of hepatocellular carcinoma.

**Pathology**

*Image: “Intermediate magnification micrograph of hepatocellular carcinoma the most common form of primary liver cancer, i.e. the most common form of cancer to arise in the liver.” by Nephron. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0)*

**Hepatocellular carcinoma may present as:**
1. A large solitary mass
2. A multinodular lesion with nodules of variable sizes
3. Diffusely infiltrative cancer sometimes involving the entire liver

All of these forms can result in enlargement of the liver and thus present with symptoms similar to other liver diseases.

Under microscopic examination, this cancer will show abnormal liver cells with variable degrees of differentiation. The well-differentiated cells will look similar to the hepatocytes arranged in cords separated by sinusoids. They can also have a green discoloration which indicates that these cells are so well differentiated that they are capable of producing bile.

The undifferentiated cells will appear as sheets of anaplastic cells. It is often difficult to distinguish a poorly differentiated hepatocellular carcinoma from a metastatic tumor.

These cancers can metastasize extensively through the hepatic or portal veins to the lymph nodes, bones and lungs. Metastasis of cancer tends to occur early in the lymphatic system to regional lymph nodes. Hematogenous spread to the lung occurs late in the disease. Sometimes long, snake like masses of the tumor spread along the portal vein or the hepatic vein in to the inferior vena cava and up to the right atrium.

Hepatocellular carcinoma commonly secretes alpha fetoprotein (AFP) into the blood. Elevated serum AFP levels are found in at over 50% of the patients with hepatocellular carcinoma – making it an important diagnostic test.

A variant of hepatocellular carcinoma is fibrolamellar carcinoma, which has a better prognosis than hepatocellular carcinoma. Fibrolamellar carcinoma usually will not have an underlying chronic liver cell disease. This tumor occurs in both males and females equally, in the age range of 20 to 40 years. It presents as a hard scirrhus tumor with fibrous bands going through it. Histologically, it appears as well differentiated polygonal cells separated by dense collagen bands.

Clinical features

Clinical features include:

- Weight loss
- Anorexia
- Fever
- Right upper quadrant pain
- Ascites

If the above symptoms newly appear in a known patient with cirrhosis, then hepatocellular carcinoma should be suspected.

Diagnosis

- Serum alpha fetoprotein concentration – may be increased but can be normal in one-third of the patients.
- Ultrasound
- Enhanced CT – helps identify hepatocellular carcinoma but not usually helpful for small lesions less than 1cm.
- MRI
- Tumor biopsy under ultrasound guidance – This is not used frequently even though it helps to come to a diagnosis because imaging techniques are often...
sufficient to make a diagnosis of hepatocellular carcinoma.

**Treatment**

- **Surgical resection** - This is only considered if the lesion is a solitary nodule less than 5 cm in size or up to 3 lesions each with a size less than 3 cm. Although there is a risk of recurrence, surgical resection of the tumor provides a median survival of 5 years.
- **Liver transplantation** - This is the only option available to provide a complete cure to patients with a small primary tumor.
- **Transarterial embolization or radiofrequency ablation** - although this is less successful than surgical excision, it can prolong the survival period in patients with small primary tumors and good liver function.
- **Antiangiogenic compounds such as sorafenib** - this helps to prolong survival in patients with non-resectable tumors.

**Cholangiocarcinoma (CCA)**

Cholangiocarcinoma is the second most common malignant primary liver tumor. It arises from the bile ducts within and outside of the liver and is not associated with liver cirrhosis.

The risk factors for cholangiocarcinoma include primary sclerosing cholangitis, congenital fibropolycystic diseases of the biliary system, and HCV infection.

Cholangiocarcinomas are classified as intrahepatic or extrahepatic; 80% to 90% of all CCAs are extrahepatic.

Extrahepatic CCAs are usually small at the time of diagnosis. They appear as firm, grey nodules within the bile duct wall. Most of them are adenocarcinomas and may or may not secrete mucin. The presence of mucin in the cytoplasm helps to distinguish them from a hepatocellular carcinoma.

Intrahepatic CCAs occur in a non-cirrhotic liver and tracks down the portal tracts forming a tree-like tumor within the liver.

Patients with cholangiocarcinoma are often presented in a similar way as hepatocellular carcinoma. However, jaundice is more frequent in CCAs, because of bile duct obstruction. In these patients, surgical resection is rarely possible and the prognosis is poor (mean survival is 6 months from diagnosis).
Liver metastasis (secondary hepatic carcinoma)

Metastatic (secondary) tumors of the liver are most common type of hepatic neoplasm. The most common sources are cancers of the **colon, breast, lung, and pancreas**. However, any malignant tumor can metastasize to the liver.

In metastatic cancers, multiple lesions are usually seen with massive hepatomegaly.

It is very difficult to distinguish between hepatocellular carcinoma and metastatic liver tumor. **Features that can help to differentiate between the two include:**

1. Often, the nodules of the liver show central necrosis and umbilication seen macroscopically
2. Presence of cirrhosis favors hepatocellular carcinoma
3. Increased levels of AFP are diagnostic of hepatocellular carcinoma.
4. If the tumor has invaded the hepatic veins, then this feature also favors hepatocellular carcinoma.

References


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