What is Liver Cancer?

This discussion deals only with **adult primary liver cancer.** Primary liver cancer is cancer that begins in the liver. Adult primary liver cancer is rare in the United States. Usually, when the liver is affected by cancer, it is because cancer that started in a different part of the body—the pancreas, colon, stomach, breast, or lung, for example—has spread (metastasized) to the liver. These cancers are not **primary liver cancer** but, rather, are named for the part of the body in which they originated. For example, breast cancer that has metastasized to the liver is called "metastatic breast cancer" or "secondary liver cancer."

The liver is the largest organ in the body, and its functions are vital to the digestion of food. No one can survive without a liver. The liver does the following:

- Collects and filters blood from the intestine.
- Processes and stores needed nutrients absorbed from the intestines.
- Chemically changes (metabolizes) some nutrients before they can be used by the rest of the body for energy or to repair and build tissue.
- Produces some of the clotting factors needed in the blood stream.
- Removes toxic wastes from the body.
- Helps maintain the proper sugar level in the body.

As we well know, there are many kinds of cancer; unfortunately they all come about because of the out-of-control growth of abnormal cells.

What is hepatocellular carcinoma (HCC)?

Hepatocellular carcinoma is a cancer arising from the liver. It is also known as primary liver cancer or hepatoma. The liver is made up of different cell types (e.g., bile ducts, blood vessels, and fat-storing cells). However, liver cells (hepatocytes) make up 80% of the liver tissue. Thus, the majority of primary liver cancers (over 90 to 95%) arises from liver cells and is called hepatocellular cancer or carcinoma.

When patients or physicians speak of liver cancer, however, they are often referring to cancer that has spread to the liver, having originated in other organs (such as the colon, stomach, pancreas, breast, and lung). More specifically, this type of liver cancer is called metastatic liver disease (cancer) or secondary liver cancer. Thus, the term liver cancer actually can refer to either metastatic liver cancer or hepatocellular cancer. The subject of this article is hepatocellular carcinoma, which I will refer to as HCC.

What is the scope of the HCC problem?

HCC is the fifth most common cancer in the world. A deadly cancer, HCC will kill almost all patients who have it within a year. In 1990, the World Health Organization estimated that there were about 430,000 new cases of HCC worldwide, and a similar number of patients died as a result of this disease. About three quarters of the cases of HCC are found in Southeast Asia (China, Hong Kong, Taiwan, Korea, and Japan). HCC is also very common in sub-Saharan Africa (Mozambique and South Africa).

The frequency of HCC in Southeast Asia and sub-Saharan Africa is greater than 20 cases per 100,000 population. In contrast, the frequency of HCC in North America and Western Europe is much lower, less than 5 per 100,000 population. However, the frequency of HCC among native Alaskans is comparable to that seen in Southeast Asia. Moreover, recent data show that the frequency of HCC in the U.S. overall is rising. This increase is due primarily to chronic hepatitis C, an infection of the liver that causes HCC.

What are the population characteristics (epidemiology) of HCC?

In the U.S. the highest frequency of HCC occurs in immigrants from Asian countries, where HCC is common. The frequency of HCC among Caucasians is the lowest, whereas among African-Americans and Hispanics, it is intermediate. The frequency of HCC is high among Asians because HCC is closely linked to chronic hepatitis B infection. This is especially so in individuals who have been infected with chronic hepatitis B for most of their lives. If you take a world map depicting the frequency of chronic hepatitis B infection, you can easily superimpose that map on a map showing the frequency of HCC.

The initial presentation (symptoms) of HCC in patients in areas of high HCC frequency is quite different from that seen in low frequency areas. Patients from high frequency areas usually start developing HCC in their 40's, and the cancer is usually more aggressive. That is, the HCC presents with severe symptoms and is inoperable (too advanced for surgery) at the time of diagnosis. Also, in these areas, the frequency of HCC is three to four times higher in men than in women, and most of these patients are infected with chronic hepatitis B. In contrast, HCC in lower risk areas occurs in patients in their 50's and 60's and the predominance of men is less striking.

What are the risk factors for HCC?

Hepatitis B infection

The role of hepatitis B virus (HBV) infection in causing HCC is well established. Several lines of evidence point to this strong association. As noted earlier, the frequency of HCC relates to (correlates with) the frequency of chronic HBV infection. In addition, the patients with HBV who are at greatest risk for HCC are men with HBV cirrhosis (scarring of the liver) and a family history of HCC. Perhaps the most convincing evidence, however, comes from a prospective (looking forward in time) study done in the 1970's in Taiwan involving male government employees over the age of 40. In this study, the investigators found that the risk of developing HCC was 200 times higher among employees who had chronic HBV as compared to employees without chronic HBV!

Studies in animals also have provided evidence that HBV can cause HCC. For example, we have learned that HCC develops in other mammals that are naturally infected with HBV-related viruses. Finally, by infecting transgenic mice with certain parts of the hepatitis B virus, scientists caused HCC to develop in mice that do not usually develop liver cancer. (Transgenic mice are mice that have been injected with new or foreign genetic material.)

How does chronic HBV cause HCC? In patients with both chronic HBV and HCC, the genetic material of HBV is frequently found to be part of the genetic material of the cancer cells. It is thought, therefore, that specific regions of the HBV genome (genetic code) enter the genetic material of the liver cells. This HBV genetic material may then disrupt the normal genetic material in the liver cells, thereby causing the liver cells to become cancerous.

The vast majority of HCC that is associated with chronic HBV occurs in individuals who have been infected most of their lives. In areas where HBV is not always present (endemic) in the community (e.g., the U.S.), HCC is relatively uncommon. The reason for this is that most of the people with chronic HBV in these areas acquired the infection as adults. However, HCC can develop in individuals who acquired chronic HBV in adulthood if there are other risk factors, such as chronic alcohol use or co-infection with chronic HCV infection.

Hepatitis C infection

Hepatitis C virus (HCV) infection is also associated with the development of HCC. In fact, in Japan, HCV is present in up to 75% of cases of HCC. As with HBV, the majority of HCV patients with HCC have associated cirrhosis (liver scarring). In several retrospective-prospective studies (looking backward and forward in time) of the natural history of hepatitis C, the average time to develop HCC after exposure to HCV was about 28 years. The HCC occurred about 8 to 10 years after the development of cirrhosis in these patients with hepatitis C. Several prospective European studies report that the annual incidence (occurrence over time) of HCC in cirrhotic HCV patients ranges from 1.4 to 2.5% per year.

In HCV patients, the risk factors for developing HCC include the presence of cirrhosis, older age, male gender, elevated baseline alpha-fetoprotein level (a blood tumor marker), alcohol use, and co-infection with HBV. Some earlier studies suggested that HCV genotype 1b (a common genotype in the U.S.) may be a risk factor, but more recent studies do not support this finding.

The way in which HCV causes HCC is not well understood. Unlike HBV, the genetic material of HCV is not inserted directly into the genetic material of the liver cells. It is known, however, that cirrhosis from any cause is a risk factor for the development of HCC. It has been argued, therefore, that HCV, which causes cirrhosis of the liver, is an indirect cause of HCC.

On the other hand, there are some chronic HCV infected individuals who have HCC without cirrhosis. So, it has been suggested that the core (central) protein of HCV is the culprit in the development of HCC. The core protein itself (a part of the hepatitis C virus) is thought to impede the natural process of cell death or interfere with the function of a

normal tumor suppressor (inhibitor) gene (the p53 gene). The result of these actions is that the liver cells go on living and reproducing without the normal restraints, which is what happens in cancer.

Alcohol

Cirrhosis caused by chronic alcohol consumption is the most common association of HCC in the developed world. Actually, we now understand that many of these cases are also infected with chronic HCV. The usual setting is an individual with alcoholic cirrhosis who has stopped drinking for ten years, and then develops HCC. It is somewhat unusual for an actively drinking alcoholic to develop HCC. What happens is that when the drinking is stopped, the liver cells try to heal by regenerating (reproducing). It is during this active regeneration that a cancer-producing genetic change (mutation) can occur, which explains the occurrence of HCC after the drinking has been stopped.

Patients who are actively drinking are more likely to die from non-cancer related complications of alcoholic liver disease (e.g., liver failure). Indeed, patients with alcoholic cirrhosis who die of HCC are about 10 years older than patients who die of non-cancer causes. Finally, as noted above, alcohol adds to the risk of developing HCC in patients with chronic HCV or HBV infections.

Aflatoxin B1

Aflatoxin B1 is the most potent liver cancer-forming chemical known. It is a product of a mold called Aspergillus flavus, which is found in food that has been stored in a hot and humid environment. This mold is found in such foods as peanuts, rice, soybeans, corn, and wheat. Aflatoxin B1 has been implicated in the development of HCC in Southern China and Sub-Saharan Africa. It is thought to cause cancer by producing changes (mutations) in the p53 gene. These mutations work by interfering with the gene's important tumor suppressing (inhibiting) functions.

Drugs, medications, and chemicals

There are no medications that cause HCC, but female hormones (estrogens) and protein-building (anabolic) steroids are associated with the development of hepatic adenomas. These are benign liver tumors that may have the potential to become malignant (cancerous). Thus, in some individuals, hepatic adenoma can evolve into cancer.

Certain chemicals are associated with other types of cancers found in the liver. For example, thorotrast, a previously used contrast agent for imaging, caused a cancer of the blood vessels in the liver called hepatic angiosarcoma. Also, vinyl chloride, a compound used in the plastics industry, can cause hepatic angiosarcomas that appear many years after the exposure.

Hemochromatosis

HCC will develop in up to 30% of patients with hereditary hemochromatosis . Patients at the greatest risk are those who develop cirrhosis with their hemochromatosis. Unfortunately, once cirrhosis is established, effective removal of excess iron (the

treatment for hemochromatosis) will not reduce the risk of developing HCC.

Cirrhosis

Individuals with most types of cirrhosis of the liver are at an increased risk of developing HCC. In addition to the conditions described above (hepatitis B, hepatitis C, alcohol, and hemochromatosis), alpha 1 anti-trypsin deficiency, a hereditary condition that can cause emphysema and cirrhosis, may lead to HCC. Liver cancer is also strongly associated with hereditary tyrosinemia, a childhood biochemical abnormality that results in early cirrhosis.

Certain causes of cirrhosis are less frequently associated with HCC than are other causes. For example, HCC is rarely seen with the cirrhosis in Wilson's disease (abnormal copper metabolism) or primary sclerosing cholangitis (chronic scarring and narrowing of the bile ducts). It used to be thought that HCC is rarely found in primary bilary cirrhosis (PBC) as well. Recent studies, however, show that the frequency of HCC in PBC is comparable to that in other forms of cirrhosis.

What are the symptoms of HCC?

The initial symptoms (the clinical presentations) of HCC are variable. In countries where HCC is very common, the cancer generally is discovered at a very advanced stage of disease for several reasons. For one thing, areas where there is a high frequency of HCC are generally developing countries where access to healthcare is limited. For another, screening examinations for patients at risk for developing HCC are not available in these areas. In addition, patients from these regions actually have more aggressive HCC disease. In other words, the tumor usually reaches an advanced stage and causes symptoms more rapidly. In contrast, patients in areas of low HCC frequency tend to have HCC tumors that progress more slowly and, therefore, remain without symptoms longer.

Abdominal pain is the most common symptom of HCC and usually signifies a very large tumor or widespread involvement of the liver. Additionally, unexplained weight loss or unexplained fevers are warning signs of HCC in patients with cirrhosis. These symptoms are less common in individuals with HCC in the U.S. because these patients are usually diagnosed at an earlier stage. However, whenever the overall health of a patient with cirrhosis deteriorates, every effort should be made to look for HCC.

A very common initial presentation of HCC in a patient with compensated cirrhosis (no complications of liver disease) is the sudden onset of a complication. For example, the sudden appearance of ascites (abdominal fluid and swelling), jaundice (yellow color of the skin), or muscle wasting without causative (precipitating) factors (e.g., alcohol consumption) suggests the possibility of HCC. What's more, the cancer can invade and block the portal vein (a large vein that brings blood to the liver from the intestine and spleen). When this happens, the blood will travel paths of less resistance, such as through esophageal veins. This causes increased pressure in these veins, which results in dilated (widened) veins called esophageal varices. The patient then is at risk for hemorrhage from the rupture of the varices into the gastrointestinal tract. Rarely, the cancer itself can rupture and bleed into the abdominal cavity, resulting in bloody ascites.

On physical examination, an enlarged, sometimes tender, liver is the most common

finding. HCCs are very vascular (containing many blood vessels) tumors. Thus, increased amounts of blood feed into the hepatic artery (artery to the liver) and cause turbulent blood flow in the artery. The turbulence results in a distinct sound in the liver (hepatic bruit) that can be heard with a stethoscope in about one quarter to one half of patients with HCC. Any sign of advanced liver disease (e.g., ascites, jaundice, or muscle wasting) means a poor prognosis. Rarely, a patient with HCC can become suddenly jaundiced when the tumor erodes into the bile duct. The jaundice occurs in this situation because both sloughing of the tumor into the duct and bleeding that clots in the duct can block the duct.

In advanced HCC, the tumor can spread locally to neighboring tissues or, through the blood vessels, to elsewhere in the body (distant metastasis). Locally, HCC can invade the veins that drain the liver (hepatic veins). The tumor can then block these veins, which results in congestion of the liver. The congestion occurs because the blocked veins cannot drain the blood out of the liver. (Normally, the blood in the hepatic veins leaving the liver flows through the inferior vena cava, which is the largest vein that drains into the heart.) In African patients, the tumor frequently blocks the inferior vena cava. Blockage of either the hepatic veins or the inferior vena cava results in a very swollen liver and massive formation of ascites. In some patients, as previously mentioned, the tumor can invade the portal vein and lead to the rupture of esophageal varices.

Regarding the distant metastases, HCC frequently spreads to the lungs, presumably by way of the blood stream. Usually, patients do not have symptoms from the lung metastases, which are diagnosed by radiologic (x-ray) studies. Rarely, in very advanced cases, HCC can spread to the bone or brain.

Healthy Cells vs. Cancer Cells

Healthy cells are like a cat. They need structure to determine the size of bones and shape of the body, tail and whiskers. The DNA in genes and chromosomes determine this. They need energy to play and prowl and sustain life. This is derived from chemicals in food. Cats need a system to deliver chemicals (food nutrients like amino acids, carbohydrates, fats, vitamins and minerals) to all parts of their body. These are the blood vessels. Growth factors take a kitten into a lazy old cat, all the while helping it to function normally.

The body and its cells are mostly made up of protein. The building blocks of proteins are substances called amino acids that in the form of enzymes and hormones literally control every chemical reaction within the cells. When these are modified, different messages are sent to a complex control system that can alter their function. There are twenty different kinds of amino acids that are essential to life. Twelve of these can be synthesized within the body however; eight must be supplied by the daily diet.

Structure	
Normal Cells	**Cancer Cells**
DNA in genes and chromosomes go about their business in a normal way.	Cancer cells develop a different DNA or gene structure or acquire abnormal numbers of chromosomes.
Cells divide in an orderly way to produce more cells only when the body needs	Cells continue to be created without control or order. If not needed, a mass of tissue is

them.	formed which is called a tumor.
Energy	
Normal Cells	**Cancer Cells**
Cells derive 70% of their energy from a system called the “Krebs Cycle.”	Cells have a defective “Krebs Cycle” and derive little or no energy from it.
Cells derive only 20% of their energy from a system called “Glycolosis.”	Cancer cells derive almost all their energy from “Glycolosis.”
Cells derive most of their energy with the use of oxygen.	Cells derive most of their energy in the absence of oxygen.
Blood Vessels	
Normal Cells	**Cancer Cells**
Cells have a built-in blood vessel system.	Cells do not have a built-in blood vessel system. They require more of certain amino acids to grow.

Growth Factors	
Normal Cells	**Cancer Cells**
While similar to cancer cells, the amount of them is more in balance to produce a more normal level of activity.	These cells have over produced, require more chemicals (food) and are over active.
Functions	
Normal Cells	**Cancer Cells**
The enzymes and hormones go about business in a normal balanced manner.	The enzymes and hormones are either over active or under active.
Tumors are Different	
Benign	**Malignant**
Benign tumors are not cancerous. They do not invade nearby tissues nor spread to other parts of the body. They can be removed and are not a threat to life.	Malignant tumors are cancerous. They can invade and damage nearby tissues and organs and they can break away and enter the blood stream to form new tumors in other parts of the body. The spread of cancer is called metastasis.

How is HCC diagnosed?

Blood tests

Liver cancer is not diagnosed by routine blood tests, including a standard panel of liver tests. This is why the diagnosis of HCC depends so much on the vigilance of the physician screening with a tumor marker (alpha-fetoprotein) in the blood and radiological imaging studies. Since most patients with HCC have associated liver disease (cirrhosis), their liver blood tests may not be normal to begin with. If these blood tests become abnormal or worsen due to HCC, this usually signifies extensive cancerous involvement of the liver. At that time, any medical or surgical treatment would be too late.

Sometimes, however, other abnormal blood tests can indicate the presence of HCC. Remember that each cell type in the body contains the full complement of genetic

information. What differentiates one cell type from another is the particular set of genes that are turned on or off in that cell. When cells become cancerous, certain of the cell's genes that were turned off may become turned on. Thus, in HCC, the cancerous liver cells may take on the characteristics of other types of cells. For example, HCC cells sometimes can produce hormones that are ordinarily produced in other body systems. These hormones then can cause certain abnormal blood tests, such as a high red blood count (erythrocytosis), low blood sugar (hypoglycemia) and high blood calcium (hypercalcemia).

Another abnormal blood test, high serum cholesterol (hypercholesterolemia), is seen in up to 10% of patients from Africa with HCC. The high cholesterol occurs because the liver cancer cells are not able to turn off (inhibit) their production of cholesterol. (Normal cells are able to turn off their production of cholesterol.)

There is no reliable or accurate screening blood test for HCC. The most widely used biochemical blood test is alpha-fetoprotein (AFP), which is a protein normally made by the immature liver cells in the fetus. At birth, infants have relatively high levels of AFP, which fall to normal adult levels by the first year of life. Also, pregnant women carrying babies with neural tube defects may have high levels of AFP. (A neural tube defect is an abnormal fetal brain or spinal cord that is caused by folic acid deficiency during pregnancy.)

In adults, high blood levels (over 500 nanograms/milliliter) of AFP are seen in only three situations:

- HCC
- Germ cell tumors (cancer of the testes and ovaries)
- Metastatic cancer in the liver (originating in other organs)

Several assays (tests) for measuring AFP are available. Generally, normal levels of AFP are below 10 ng/ml. Moderate levels of AFP (even almost up to 500 ng/ml) can be seen in patients with chronic hepatitis. Moreover, many patients with various types of acute and chronic liver diseases without documentable HCC can have mild or even moderate elevations of AFP.

The sensitivity of AFP for HCC is about 60%. In other words, an elevated AFP blood test is seen in about 60% of HCC patients. That leaves 40% of patients with HCC who have normal AFP levels. Therefore, a normal AFP does not exclude HCC. Also, as noted above, an abnormal AFP does not mean that a patient has HCC. It is important to note, however, that patients with cirrhosis and an abnormal AFP, despite having no documentable HCC, still are at very high risk of developing HCC. Thus, any patient with cirrhosis and an elevated AFP, particularly with steadily rising blood levels, will either most likely develop HCC or actually already have an undiscovered HCC.

An AFP greater than 500 ng/ml is very suggestive of HCC. In fact, the blood level of AFP loosely relates to (correlates with) the size of the HCC. Finally, in patients with HCC and abnormal AFP levels, the AFP may be used as a marker of response to treatment. For example, an elevated AFP is expected to fall to normal in a patient whose HCC is successfully removed surgically (resected).

There are a number of other HCC tumor markers that currently are research tools and

not generally available. These include des-gamma-carboxyprothrombin (DCP), a variant of the gamma-glutamyltransferase enzymes, and variants of other enzymes (e.g., alpha-L-fucosidase), which are produced by normal liver cells. (Enzymes are proteins that speed up biochemical reactions.) Potentially, these blood tests, used in conjunction with AFP, could be very helpful in diagnosing more cases of HCC than with AFP alone.

Imaging studies

Imaging studies play a very important role in the diagnosis of HCC. A good study can provide information as to the size of the tumor, the number of tumors, and whether the tumor has involved major blood vessels locally or spread outside of the liver. There are several types of studies, each having its merits and disadvantages. In practice, several studies combined often complement each other. On the other hand, a plain X-ray is not very helpful, and therefore, is not routinely done in the diagnostic work-up of HCC. Further, there is no practical role for nuclear medicine scans of the liver and spleen in the work-up for HCC. Such scans are not very sensitive and they provide no additional information beyond that provided by the other (ulrtasound, CT, and MRI) scans.

Ultrasound examination is usually the first study ordered if HCC is suspected in a patient. The accuracy of an ultrasound depends very much on the technician and radiologist who perform the study (operator dependent). Studies from Japan and Taiwan report that ultrasound is the most sensitive imaging study for diagnosing and characterizing HCC. But you should know that in these studies, highly experienced individuals performed the scans and spent up to one hour scanning each patient suspected of having HCC. An ultrasound has the advantages of not requiring intravenous contrast material and not involving radiation. Moreover, the price of an ultrasound is quite low as compared to the other types of scans.

Computerized axial tomography (CT scan) is a very common study used in the U.S. for the work-up of tumors in the liver. The ideal CT study is a multi-phase, spiral CT scan using oral and intravenous contrast material. Pictures are taken in three phases:

- Without intravenous contrast
- With intravenous contrast (enhanced imaging) that highlights the arterial system (arterial phase)
- When the contrast is in the venous phase

The pictures are taken at very frequent intervals (thin slices) as the body is moved through the CT scanner. Many radiologists use a specific protocol that determines how the contrast is infused in relation to how the pictures are taken. Therefore, CT is much less operator-dependent than is ultrasound. However, CT is considerably more expensive. Furthermore, CT requires the use of contrast material, which has the potential risks of an allergic reaction and adverse effects on kidney function.

There are several variations to CT scanning. For example, in a CT angiogram, which is a highly invasive (enters a part of the body) study, intravenous contrast is selectively infused through the hepatic artery (artery to the liver). The purpose is to highlight the vessels for better visualization of them by the CT scan. Also, in Japan, an oily contrast material called lipiodol, which is selectively taken up by HCC cells, has been used with CT. The purpose of this approach is to improve the sensitivity of the scan. That is to say,

the goal is to increase the percentage of abnormal CT scans in patients who have HCC.

Magnetic Resonance Imaging (MRI) can provide very clear images of the body. Its advantage over CT is that MRI can provide sectional views of the body in different planes. The technology has evolved to the point that the newer MRIs can actually reconstruct images of the biliary tree (bile ducts and gallbladder) and of the arteries and veins of the liver. (The biliary tree transports bile from the liver to the duodenum, the first part of the intestine.) MRI studies can be made even more sensitive by using intravenous contrast material (e.g., gadolinium).

MRI scans are very expensive and there is tremendous variability in the quality of the images. The quality depends on the age of the machine and the ability of the patients to hold their breath for up to 15 to 20 seconds at a time. Furthermore, many patients, because of claustrophobia, cannot tolerate being in the MRI scanner. However, the current open MRI scanners generally do not provide as high quality images as the closed scanners do.

Advances in ultrasound, CT, and MRI technology have almost eliminated the need for angiography. An angiography procedure involves inserting a catheter into the femoral artery (in the groin) through the aorta, and into the hepatic artery, the artery that supplies blood to the liver. Contrast material is then injected, and X-ray pictures of the arterial blood supply to the liver are taken. An angiogram of HCC shows a characteristic blush that is produced by newly formed abnormal small arteries that feed the tumor (neovascularization).

What, then, is the best imaging study for diagnosing HCC? There is no simple answer. Many factors need to be taken into consideration. For example, is the diagnosis of HCC known or is the scan being done for screening? What is the expertise of doctors in the patient's area? What is the quality of the different scanners at a particular facility? Are there economic considerations? Does the patient have any other conditions that need to be considered, such as claustrophobia or kidney impairment? Does the patient have any hardware, e.g., a pacemaker or metal prosthetic device? (The hardware would make doing an MRI impossible.)

If you live in Japan or Taiwan and have access to a radiologist or hepatologist with expertise in ultrasound, then it may be as good as a CT scan. Ultrasound is also the most practical (easier and cheaper) for regular screening (surveillance). In North America, a multi-phase spiral CT scan is probably the most accurate type of scan. However, for patients with impaired renal function or who have access to a state-of-the-art MRI scanner, the MRI may be the diagnostic scan of choice. Finally, keep in mind that the technology of ultrasound, CT, and MRI is ever evolving with the development of better machines and the use of special contrast materials to further characterize the tumors.

Liver biopsy or aspiration

In theory, a definitive diagnosis of HCC is always based on microscopic (histological) confirmation. However, some liver cancers are well differentiated, which means they are made up of nearly fully developed, mature liver cells (hepatocytes). Therefore, these cancers can look very similar to non-cancerous liver tissue under a microscope. Moreover, not all pathologists are trained to recognize the subtle differences between

well-differentiated HCC and normal liver tissue. Also, some pathologists can mistake HCC for adenocarcinoma in the liver. An adenocarcinoma is a different type of cancer, and, as previously mentioned, it originates from outside of the liver. Most importantly, a metastatic adenocarcinoma would be treated differently from a primary liver cancer (HCC). Therefore, all of this considered, it is important that an expert liver pathologist review the tissue slides of liver tumors in questionable situations.

Tissue can be sampled with a very thin needle. This technique is called fine needle aspiration. When a larger needle is used to obtain a core of tissue, the technique is called a biopsy. Generally, radiologists, using ultrasound or CT scans to guide the placement of the needle, perform the biopsies or fine needle aspirations. The most common risk of the aspiration or biopsy is bleeding, especially because HCC is a tumor that is very vascular (contains many blood vessels). Rarely, new foci (small areas) of tumor can be seeded (planted) from the tumor by the needle into the liver along the needle track.

The aspiration procedure is safer than a biopsy with less risk for bleeding. However, interpretation of the specimen obtained by aspiration is more difficult because often only a cluster of cells is available for evaluation. Thus, a fine needle aspiration requires a highly skilled pathologist. Moreover, a core of tissue obtained with a biopsy needle is more ideal for a definitive diagnosis because the architecture of the tissue is preserved. The point is that sometimes a precise diagnosis can be important clinically. For example, some studies have shown that the degree of differentiation of the tumor may predict the patient's outcome (prognosis). That is to say, the more differentiated (resembling normal liver cells) the tumor is, the better the prognosis.

All of that said, in many instances, there is probably no need for a tissue diagnosis by biopsy or aspiration. If a patient has a risk factor for HCC (e.g., cirrhosis, chronic hepatitis B, or chronic hepatitis C) and a significantly elevated alpha-fetoprotein blood level, the doctor can be almost certain that the patient has HCC without doing a biopsy. The patient and physician should always ask two questions before deciding on doing a liver biopsy:

1. Is this tumor most likely an HCC?
2. Will the biopsy findings change the management of the patient?

If the answer to both questions is yes, then the biopsy should be done. Finally, there are two other situations related to HCC in which a biopsy may be considered. The first is to characterize a liver abnormality (e.g., a possible tumor) seen by imaging in the absence of risk factors for HCC or elevated alpha-fetoprotein. The second is to determine the extent of disease when there are multiple areas of abnormalities (possibly tumors) seen by imaging in the liver.

Overall, no blanket recommendation can be given regarding the need for liver biopsy or aspiration. The decision has to be made on an individual basis, depending on the treatment options and the expertise of the medical and surgical teams.

What is the natural history of HCC?

The natural history of HCC depends on the stage of the tumor and the severity of associated liver disease (e.g., cirrhosis) at the time of diagnosis. For example, a patient with a 1 cm tumor with no cirrhosis has a greater than 50% chance of surviving 3 years, even without treatment. In contrast, a patient with multiple tumors involving both lobes of the liver (multicentric tumors) with decompensated cirrhosis (signs of liver failure) is unlikely to survive more than 6 months, even with treatment.

What are the predictors of a poor outcome? Our knowledge of the prognosis is based on studying many patients with HCC, separating out their clinical characteristics, and relating them to the outcome. Grouped in various categories, the unfavorable clinical findings include;

- Population characteristics (demographics); male gender, older age, or alcohol consumption.
- Symptoms; weight loss or decreased appetite.
- Signs of impaired liver function; jaundice, ascites, or encephalopathy (altered mental state).
- Blood tests; elevated liver tests (bilirubin or transaminase), reduced albumin, elevated AFP, elevated blood urea nitrogen (BUN), or low serum sodium.
- Staging of tumor (based on imaging or surgical findings); more than one tumor, tumor over 3cm (almost 1¼ inches), tumor invasion of local blood vessels (portal and/or hepatic vein), tumor spread outside of the liver (to lymph nodes or other organs).

There are various systems for staging HCC. Some systems look at clinical findings while others rely solely on pathological (tumor) characteristics. It makes the most sense to use a system that incorporates a combination of clinical and pathological elements. In any event, it is important to stage the cancer because staging can provide guidelines not only for predicting outcome (prognosis) but also for decisions regarding treatment.

The doubling time for a cancer is the time it takes for the tumor to double in size. For liver cancer, the doubling time is quite variable, ranging from one month to eighteen months. This kind of variability tells us that every patient with HCC is unique. Therefore, an assessment of the natural history and the evaluation of different treatments are very difficult. Nevertheless, in patients with a solitary HCC that is less than 3 cm, with no treatment, we can expect that 90% of the patients will survive (live) for one year, 50% for three years, and 20% for five years. In patients with more advanced disease, we can expect that 30% will survive for one year, 8% for three years, and none for five years.

What are the treatment options for HCC?

The treatment options are dictated by the stage of HCC and the overall condition of the patient. The only proven cure for HCC is liver transplantation for a solitary, small (<3cm) tumor. Now, many physicians may dispute this statement. They may argue that a small tumor can be surgically removed (partial hepatic resection) without the need for a liver transplantation. Moreover, they may claim that the one and three year survival rates for resection are perhaps comparable to those for liver transplantation.

However, most patients with HCC also have cirrhosis of the liver and would not tolerate liver resection surgery. But, they probably could tolerate the transplantation operation,

which involves removal of the patient's entire diseased liver just prior to transplanting a donor liver. Furthermore, many patients who undergo hepatic resections will develop a recurrence of HCC elsewhere in the liver within several years. In fact, some experts believe that once a liver develops HCC, there is a tendency for that liver to develop other tumors at the same time (synchronous multicentric occurrence) or at a later time (metachronous multicentric occurrence).

The results of the various medical treatments (chemotherapy, chemoembolization, ablation, and proton beam therapy) remain disappointing. Moreover, for reasons noted earlier (primarily the variability in natural history), there have been no systematic study comparisons of the different treatments. As a result, individual patients will find that the various treatment options available to them depend largely on the local expertise.

How do we know if a particular treatment worked for a particular patient? Well, hopefully, the patient will feel better. However, a clinical response to treatment is usually defined more objectively. Thus, a response is defined as a decrease in the size of the tumor on imaging studies along with a reduction of the alpha-fetoprotein in the blood, if the level was elevated prior to treatment.

Chemotherapy

Systemic (entire body) chemotherapy

The most commonly used systemic chemotherapeutic agents are doxorubicin (Adriamycin) and 5-fluorouracil (5 FU). These drugs are used together or in combination with new experimental agents. These drugs are quite toxic and results have been disappointing. A few studies suggest some benefit with tamoxifen (Nolvadex) but just as many studies show no advantage. Octreotide (Sandostatin) given as an injection was shown in one study to slow down the progression of large HCC tumors, but so far, no other studies have confirmed this benefit.

Hepatic arterial infusion of chemotherapy

The normal liver gets its blood supply from two sources; the portal vein (about 70%) and the hepatic artery (30%). However, HCC gets its blood exclusively from the hepatic artery. Making use of this fact, investigators have delivered chemotherapy agents selectively through the hepatic artery directly to the tumor. The theoretical advantage is that higher concentrations of the agents can be delivered to the tumors without subjecting the patients to the systemic toxicity of the agents.

In reality, however, much of the chemotherapeutic agents does end up in the rest of the body. Therefore, selective intra-arterial chemotherapy can cause the usual systemic (body-wide) side effects. In addition, this treatment can result in some regional side effects, such as inflammation of the gallbladder (cholecystitis), intestinal and stomach ulcers, and inflammation of the pancreas (pancreatitis). HCC patients with advanced cirrhosis may develop liver failure after this treatment. Well then, what is the benefit of intra-arterial chemotherapy? The bottom line is that fewer than 50% of patients will experience a reduction in tumor size.

An interventional radiologist (one who does therapeutic procedures) usually carries out

this procedure. The radiologist must work closely with an oncologist (cancer specialist), who determines the amount of chemotherapy that the patient receives at each session. Some patients may undergo repeat sessions at 6 to 12 week intervals. This procedure is done with the help of fluoroscopy (type of x-ray) imaging. A catheter (long, narrow tube) is inserted into the femoral artery in the groin and is threaded into the aorta (the main artery of the body). From the aorta, the catheter is advanced into the hepatic artery. Once the branches of the hepatic artery that feed the liver cancer are identified, the chemotherapy is infused. The whole procedure takes one to two hours, and then the catheter is removed.

The patient generally stays in the hospital overnight for observation. A sandbag is placed over the groin to compress the area where the catheter was inserted into the femoral artery. The nurses periodically check for signs of bleeding from the femoral artery puncture. They also check for the pulse in the foot on the side of the catheter insertion to be sure that the femoral artery is not blocked as a result of the procedure. (Blockage would be signaled by the absence of a pulse.)

Generally, the liver tests increase (get worse) during the two to three days after the procedure. This worsening of the liver tests is actually due to death of the tumor (and some non-tumor) cells. The patient may experience some post-procedure abdominal pain and low-grade fever. However, severe abdominal pain and vomiting suggest that a more serious complication has developed. Imaging studies of the liver are repeated in 6 to 12 weeks to assess the size of the tumor in response to the treatment. For more, please read the Chemotherapy article.

Chemoembolization (trans-arterial chemoembolization or TACE)

This technique takes advantage of the fact that HCC is a very vascular (contains many blood vessels) tumor and gets its blood supply exclusively from the branches of the hepatic artery. This procedure is similar to intra-arterial infusion of chemotherapy. But in TACE, there is the additional step of blocking (embolizing) the small blood vessels with different types of compounds, such as gelfoam or even small metal coils. Thus, TACE has the advantages of exposing the tumor to high concentrations of chemotherapy and confining the agents locally since they are not carried away by the blood stream. At the same time, this technique deprives the tumor of its needed blood supply, which can result in the damage or death of the tumor cells.

The type and frequency of complications of TACE and intra-arterial chemotherapy are similar. The potential disadvantage of TACE is that blocking the feeding vessels to the tumor(s) may make future attempts at intra-arterial infusions impossible. Moreover, so far, there are no head-to-head studies directly comparing the effectiveness of intra-arterial infusion versus chemoembolization. In Japan, the chemotherapeutic agents are mixed with lipiodol. The idea is that since the tumor cells preferentially take up lipiodol, they would likewise take up the chemotherapy. This Japanese technique has not yet been validated in head-to-head comparisons with conventional TACE.

What are the benefits of TACE? In one large study involving several institutions in Italy, chemoembolization did not seem to be beneficial. Patients who did not undergo TACE lived as long as patients who received TACE, even though the tumors were more likely to shrink in size in patients who were treated. Does this mean that TACE or intra-arterial chemotherapy does not work? Maybe,maybe not.

Studies in Japan have shown that TACE can downstage HCC. In other words, the tumors shrank enough to lower (improve) the stage of the cancer. From the practical point of view, shrinking the tumor creates the option for surgery in some of these patients. Otherwise, these patients had tumors that were not operable (eligible for operation) because of the initial large size of their tumors. More importantly, these same studies showed an improvement in survival in patients whose tumors became considerably smaller. In the U.S., trials are underway to see whether doing TACE before liver transplantation increases patient survival as compared to liver transplantation without TACE.

It is safe to say that TACE or intra-arterial chemoinfusion are palliative treatment options for HCC. This means that these procedures can provide relief or make the disease less severe. However, they are not curative (do not result in a cure). Fewer than 50% of patients will have some shrinkage in tumor size. Further, they can be used only in patients with relatively preserved liver function. The reason for this is that these procedures, as mentioned previously, can lead to liver failure in individuals with poor liver function.

Ablation techniques

Radiofrequency ablation (RFA) therapy

In the U.S., RFA therapy has become the ablation (tissue destruction) therapy of choice among surgeons. The surgeon can perform this procedure laparoscopically (through small holes in the abdomen) or during open exploration of the abdomen. In some instances, the procedure can be done without opening the abdomen by just using ultrasound for visual guidance.

In RFA, heat is generated locally by a high frequency, alternating current that flows from the electrodes. A probe is inserted into the center of the tumor and the non-insulated electrodes, which are shaped like prongs, are projected into the tumor. The local heat that is generated melts the tissue (coagulative necrosis) that is adjacent to the probe. The probe is left in place for about 10 to 15 minutes. The whole procedure is monitored visually by ultrasound scanning. The ideal size of an HCC tumor for RFA is less than 3 cm. Larger tumors may require more than one session. This treatment should be viewed as palliative (providing some relief), not curative.

Percutaneous ethanol (alcohol) injection

In this technique, pure alcohol is injected into the tumor through a very thin needle with the help of ultrasound or CT visual guidance. Alcohol induces tumor destruction by drawing water out of tumor cells (dehydrating them) and thereby altering (denaturing) the structure of cellular proteins. It may take up to five or six sessions of injections to completely destroy the cancer. The ideal patient for alcohol injection has fewer than three HCC tumors, each of which is:

- well defined (distinct margins)
- less than 3cm in diameter
- surrounded by a shell consisting of scar tissue (fibrous encapsulation)

- not near the surface of the liver

Additionally, patients with HCC undergoing alcohol injection should have no signs of chronic liver failure, such as ascites or jaundice. (Patients with liver failure would not be able to tolerate the alcohol injections.)

The most common side effect of alcohol injection is leakage of alcohol onto the surface of the liver and into the abdominal cavity, thereby causing pain and fever. It is important that the location of the tumor relative to the adjacent blood vessels and bile ducts is clearly identified. The reason for needing to locate these structures is to avoid injuring them during the procedure and causing bleeding, bile duct inflammation, or bile leakage.

Proton beam therapy

This technique is able to deliver high doses of radiation to a defined local area. Proton beam therapy is used in the treatment of other solid tumors as well. There are not much data yet regarding the efficacy of this treatment in HCC. The ideal patient is one with only asmall(<5 cm) solitary lesion. To have this procedure done, the patient actually is fitted with a body cast so that he or she can be placed in the identical position for each session. Therapy is conducted daily for 15 days. Preliminary data from the U.S. suggest similar effectiveness as seen with TACE or ablation therapy. It is not known, however, whether this type of radiation treatment prolongs the life of the patient.

How do these various medical treatment procedures compare to each other?

We really don't know because there are no head-to-head studies comparing chemotherapy, chemoembolization, ablation techniques, and proton beam therapy to each other. Most reports deal with a heterogeneous group of patients who have undergone only one specific treatment procedure or another. Therefore, selection of a treatment option for a particular patient will depend primarily on the expertise of the doctors in the patient's area. Studies are also needed to evaluate combinations of these procedures (e.g., proton beam and TACE). Now, what about surgery?

Surgery

Surgical options are limited to individuals whose tumors are less than 5 cm and confined to the liver, with no invasion of the blood vessels.

Liver resection

The goal of liver resection is to completely remove the tumor and the appropriate surrounding liver tissue without leaving any tumor behind. This option is limited to patients with one or two small (3cm or less) tumors and excellent liver function, ideally without associated cirrhosis. As a result of these strict guidelines, in practice, very few patients with HCC can undergo liver resection. The biggest concern about resection is that following the operation, the patient can develop liver failure. The liver failure can occur if the remaining portion of the liver is inadequate to provide the necessary support for life. Even in carefully selected patients, about 10% of them are expected to die shortly after surgery, usually as a result of liver failure.

When a portion of a normal liver is removed, the remaining liver can grow back (regenerate) to the original size within one to two weeks. A cirrhotic liver, however, cannot grow back. Therefore, before resection is performed for HCC, the non-tumor portion of the liver should be biopsied to determine whether there is associated cirrhosis.

For patients whose tumors are successfully resected, the five-year survival is about 30 to 40%. This means that 30 to 40 % of patients who actually undergo liver resection for HCC are expected to live five years. Many of these patients, however, will have a recurrence of HCC elsewhere in the liver. Moreover, it should be noted that the survival rate of untreated patients with similar sized tumors and similar liver function is probably comparable. Some studies from Europe and Japan have shown that survival rates with alcohol injection or radiofrequency ablation procedures are comparable to the survival rates of those patients who underwent resection. But again, the reader should be cautioned that there are no head-to-head comparisons of these procedures versus resection.

Liver transplantation

Liver transplantation has become an accepted treatment for patients with end-stage (advanced) liver disease of various types (e.g., chronic hepatitis B and C, alcoholic cirrhosis, primary biliary cirrhosis, and sclerosing cholangitis). Survival rates for these patients without HCC are 90% at one year, 80% at three years, and 75% at five years. Moreover, liver transplantation is the best option for patients with tumors that are less than 5cm in size who also have signs of liver failure. In fact, as one would expect, patients with small cancers (less than 3 cm) and no involvement of the blood vessels do very well. These patients have a less than 10% risk of recurrent HCC after transplant. On the other hand, there is a very high risk of recurrence in patients with tumors greater than 5 cm or with involvement of blood vessels. For these reasons, when patients are being evaluated for treatment of liver cancer, every effort should be made to characterize the tumor and look for signs of spread beyond the liver.

There is a severe shortage of organ donors in the U.S. Currently, there are about 18,000 patients on the waiting list for liver transplantation. About 4,000 donated cadaver livers (taken at the time of death) are available per year for patients with the highest priority. This priority goes to patients on the transplant waiting list who have the most severe liver failure. As a result, in many HCC patients, while they are on the waiting list, the tumor may become too large for the patient to benefit from liver transplantation. Doing palliative treatments, such as TACE, while the patient is on the waiting list for liver transplantation is currently being evaluated.

The use of a partial liver from a healthy, live donor may provide a few patients with HCC an opportunity to undergo liver transplantation before the tumor becomes too large. This innovation is a very exciting development in the field of liver transplantation.

As a precaution, doing a biopsy or aspiration of HCC should probably be avoided in patients considering liver transplantation. The reason to avoid needling the liver is that there is about a 1 to 4% risk of seeding (planting) cancer cells from the tumor by the needle into the liver along the needle track. You see, after liver transplantation, patients take powerful anti-rejection medications to prevent the patient's immune system from rejecting the new liver. However, the suppressed immune system can allow new foci (small areas) of cancer cells to multiply rapidly. These new foci of cancer cells would

normally be kept at bay by the immune cells of an intact immune system.

In summary, liver resection should be reserved for patients with small tumors and normal liver function (no evidence of cirrhosis). Patients with multiple or large tumors should receive palliative therapy with intra-arterial chemotherapy or TACE, provided they do not have signs of severe liver failure. Patients with an early stage of cancer and signs of chronic liver disease should receive palliative treatment and undergo evaluation for liver transplantation.

Is there a role for routine screening for HCC?

It makes sense to screen for HCC just as we do for colon, cervical, breast, and prostate cancer. However, the difference is that there is, as yet, no cost-effective way of screening for HCC. Blood levels of alpha-fetoprotein are normal in up to 50% of patients with small HCC. Ultrasound scanning, which is non-invasive and very safe, is, as mentioned before, operator-dependent. Therefore, the effectiveness of a screening ultrasound that is done at a small facility can be very suspect.

Even more disappointing is the fact that no study outside of Asia has shown, on a large scale, that early detection of HCC saved lives. Why is that? It is because, as already noted, the treatment for HCC, except for liver transplantation, is not very effective. Also, keep in mind that patients found with small tumors on screening live longer than patients with larger tumors only because of what is called a "lead time bias." In other words, they seem to liver longer (the bias) only because the cancer was discovered earlier (the lead time), not because of any treatment given.

Nevertheless, strong arguments can be made for routine screening. For example, the discovery of an HCC in the early stages allows for the most options for treatment, including liver resection and liver transplantation. Therefore, all patients with cirrhosis, particularly cirrhosis caused by chronic hepatitis B or C, hemochromatosis, and alcohol, should be screened at 6 to 12 month intervals with a blood alpha-fetoprotein and an imaging study. I favor alternating between an ultrasound and CT scan (or MRI). Patients with chronically (long duration) elevated alpha-fetoprotein levels warrant more frequent imaging since these patients are at even higher risk of developing HCC.

What is fibrolamellar carcinoma?

Fibrolamellar carcinoma is an HCC variant that is found in non-cirrhotic livers, usually in younger patients between the ages of 20 and 40 years. In fact, these patients have no associated liver disease and no risk factors have been identified. The alpha-fetoprotein in these patients is usually normal. The appearance of fibrolamellar carcinoma under the microscope is quite characteristic. That is, broad bands of scar tissue are seen running through the cancerous liver cells. The important thing about fibrolamellar carcinoma is that it has a much better prognosis than the common type of HCC. Thus, even with a fairly extensive fibrolamellar carcinoma, a patient can have a successful surgical removal.

Source: A.P. John Institute for Cancer Research

When considering any type of complementary cancer treatment or alternative cancer treatment, always consult with your physician first, as possible interactions could reduce your treatment protocol's efficacy.