

Liver Cancer

What Is Cancer?

Cancer develops when cells in a part of the body begin to grow out of control. Although there are many kinds of cancer, they all start because of out-of-control growth of abnormal cells.

Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide more rapidly until the person becomes an adult. After that, cells in most parts of the body divide only to replace worn-out or dying cells and to repair injuries.

Because cancer cells continue to grow and divide, they are different from normal cells. Instead of dying, they outlive normal cells and continue to form new abnormal cells.

Cancer cells often travel to other parts of the body where they begin to grow and replace normal tissue. This process, called metastasis, occurs as the cancer cells get into the bloodstream or lymph vessels of our body. When cells from a cancer like breast cancer spread to another organ like the liver, the cancer is still called breast cancer, not liver cancer.

Cancer cells develop because of damage to DNA. This substance is in every cell and directs all its activities. Most of the time when DNA becomes damaged the body is able to repair it. In cancer cells, the damaged DNA is not repaired. People can inherit damaged DNA, which accounts for inherited cancers. Many times though, a person's DNA becomes damaged by exposure to something in the environment, like smoking. Scientists still do not understand what damages a person's DNA and leads to cancer.

Cancer usually forms as a tumor. Some cancers, like leukemia, do not form tumors. Instead, these cancer cells involve the blood and blood-forming organs, and circulate through other tissues where they grow.

Remember that not all tumors are cancerous. Benign (noncancerous) tumors do not spread to other parts of the body (metastasize) and, with very rare exceptions, are not life-threatening.

Different types of cancer can behave very differently. For example, lung cancer and breast cancer are very different diseases. They grow at different rates and respond to different treatments. That is why people with cancer need treatment that is aimed at their particular kind of cancer.

Cancer is the second leading cause of death in the United States. Half of all men and one-third of all women in the U.S. will develop cancer during their lifetimes. Today, millions of people are living with cancer or have had cancer. The risk of developing most types of cancer can be reduced by changes in a person's lifestyle, for example, by quitting smoking and eating a better

diet. The sooner a cancer is found and treatment begins, the better are the chances for living for many years.

What Is Liver Cancer?

About the Liver

The liver is your largest internal organ. It lies under your right ribs just beneath your right lung and diaphragm. If you were to poke your fingers up under your right ribs, you would almost be touching it.

It is shaped like a pyramid and divided into right and left lobes. The lobes are further divided into segments. Your liver, unlike most of your other organs, receives blood from two sources. The *hepatic artery* supplies the liver with blood that is rich in oxygen. The *portal vein* carries nutrient-rich blood from the intestines.

You cannot live without your liver. It processes and stores many of the nutrients absorbed from your intestine that are necessary for your body to function. Some nutrients must be chemically changed (metabolized) in the liver before they can be used by the rest of the body for energy or to build and repair tissue. The liver produces some of the clotting factors that keep you from bleeding too much when you are cut or injured. It also secretes bile into the intestine to help absorb nutrients. The liver also plays a very important role in removing toxic wastes from the body.

The liver is made of several different types of cells. This is why several types of *malignant* (cancerous) and *benign* (noncancerous) tumors can form in the liver. These tumors have different causes, are treated differently, and have a different *prognosis* (the outlook for health or recovery).

Benign Tumors

The most common type of benign liver tumor starts in blood vessels. It is called a *hemangioma*. Because most hemangiomas of the liver cause no symptoms they do not need treatment. Some may bleed and need to be surgically removed.

Hepatic adenomas are benign tumors that start from *hepatocytes* (the main type of liver cell). Most cause no symptoms and do not need treatment. Some can cause *abdominal* (stomach area) pain, a mass in the abdomen, or blood loss and may need surgical removal. You have a much higher chance of having one of these tumors if you take birth control pills. Stopping the pills can cause the tumor to shrink.

Focal nodular hyperplasia is a tumor-like growth of several cell types (hepatocytes, bile duct cells, and connective tissue). If there are symptoms, this tumor can be surgically removed and the patient will be cured. Both focal nodular hyperplasia and hepatic adenomas are more common in women than in men.

Malignant Tumors

Angiosarcomas or hemangiosarcomas: These rare cancers begin in blood vessels of the liver. Many people who get these cancers have been exposed to vinyl chloride or to thorium dioxide (Thorotrast). Vinyl chloride is a chemical used in manufacturing some kinds of plastics. Thorotrast is a chemical that in the past was injected into some patients as part of certain x-ray tests. Once the cancer-causing properties of these chemicals were recognized, steps were taken to eliminate them or reduce their risk. Workers' exposure to vinyl chloride is now strictly regulated, and plastics manufacturing processes have been changed. Medical use of Thorotrast was stopped about 50 years ago.

Angiosarcomas grow rapidly and are usually too widespread to be removed surgically by the time they are found. Chemotherapy and radiation therapy do not help much. Most patients live less than 6 months after the diagnosis.

Cholangiocarcinoma: About 13% of primary liver cancers are cholangiocarcinomas. This cancer starts in the small bile ducts within the liver. You have a higher risk of developing this cancer if you have gallstones or gallbladder inflammation, chronic ulcerative *colitis* (a long-standing inflammation of the large bowel), or chronic infection with a parasitic worm found in parts of Asia called *Clonorchis sinensis*.

If you develop this cancer, you may have pain in your abdomen, particularly on the right side. Your liver often will become enlarged. Sometimes the cancer will start near the *hilum* of the liver (the area where bile ducts exit the liver on their way to the gallbladder) and you may develop *jaundice*, which is a yellow-green coloration of the skin and eyes. For more information, see our document on "Bile Duct Cancers."

Because they are often too big or in a part of the liver that can't be reached by surgery, most cholangiocarcinomas cannot be completely removed by surgery. Chemotherapy and radiation therapy usually don't help much. For these reasons most people with cholangiocarcinomas will live only about 6 months after the diagnosis. Surgery to bypass bile ducts blocked by cancer can temporarily relieve some symptoms.

Hepatoblastoma: Children, usually younger than 4 years old, can develop a rare kind of liver cancer called *hepatoblastoma*. The cells of hepatoblastoma are similar to fetal liver cells. About 70% of children with this disease are treated successfully and the survival rate is over 90% for early stage hepatoblastomas. Children with hepatoblastomas usually get better with chemotherapy.

Hepatocellular carcinoma: The most common form of liver cancer in adults is called *hepatocellular carcinoma* because it comes from the hepatocytes (the main type of liver cell). It accounts for about 75% of primary liver cancers. For this reason, the remaining sections of this document refer only to hepatocellular cancer (sometimes also called hepatoma).

Hepatocellular cancers can have different growth patterns.

Some begin as a single tumor that grows larger. Only late in the disease does it spread to other parts of the liver.

A second type of liver cancer spreads tentacle-like growths through the liver, almost from the beginning and is not confined to a single tumor. This is seen most often in people with liver cirrhosis; and is the most common pattern seen in the United States.

In a third type, the cancer develops as nodules in several parts of the liver.

Sometimes the pattern isn't clear and the cancer doesn't fit any of these.

Under the microscope, doctors can distinguish several subtypes of hepatocellular cancer. Of these subtypes, *fibrolamellar* is the most important. Patients with this type are usually younger than those with other subtypes. They are usually women and the rest of their noncancerous liver tissue is not diseased. This subtype has a much better prognosis than other forms of hepatocellular cancer.

Secondary liver cancer: Most of the time when cancer is found in the liver, it did not start there but spread from a cancer that developed somewhere else in the body. These *metastatic* or *secondary liver tumors* begin in other organs such as the pancreas, colon, stomach, breast, lung, etc., and *metastasize* (spread) to the liver. These tumors are named after their primary site and are further described as *metastatic*. For example, cancer that started in the lung and spread to the liver is called metastatic lung cancer. In the United States and Europe, metastatic liver tumors are more common than primary liver cancer. The opposite is true for many areas of Asia and Africa. In this document we will only discuss primary liver cancer.

What Are The Key Statistics About Liver Cancer?

The American Cancer Society estimates that 16,200 new cases (10,700 in men and 5,500 in women) of primary liver cancer and intrahepatic bile duct cancer will be diagnosed in the United States during 2001. About 14,100 people (8,900 men and 5,200 women) will die of liver cancer in the United States during 2001. In contrast to many other cancers, the number of people who develop liver cancer and die from it is increasing.

This cancer is about 10 times more common in developing countries in East Asia, Africa, and Asia. In many of these countries it is the most common type of cancer.

Since symptoms of liver cancer often do not appear until the disease is advanced, only a small number of liver cancers are found in the early stages and can be removed with surgery. Less than 30% of the patients having explorative surgery are able to have their cancer completely removed by surgery. The overall 5-year relative survival rate from liver cancer is about 10%.

The 5-year survival rate refers to the percentage of patients who live at least 5 years after their cancer is diagnosed. Five-year rates are used to produce a standard way of discussing prognosis. Of course, many people live much longer than 5 years. Five-year *relative* survival rates exclude patients dying of other diseases. This means that anyone who died of another cause, such as heart disease, is not counted.

What Are The Risk Factors For Liver Cancer?

A *risk factor* is anything that increases a person's chance of getting a disease such as cancer. Different cancers have different risk factors. For example, exposing skin to strong sunlight is a risk factor for skin cancer. Smoking is a risk factor for cancers of the lung, mouth, larynx, bladder, kidney, and several other organs. But having a risk factor, or even several, does not mean that a person will get the disease. Scientists have found several risk factors that make a person more likely to develop hepatocellular carcinoma.

Certain Types of Viral Hepatitis

Chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) is a very important liver cancer risk. These infections are responsible for making liver cancer the most common cancer in many parts of the world.

Cirrhosis

Cirrhosis is the result of scar tissue formation in the liver. This can often lead to cancer. Most liver cirrhosis in the US occurs in people who abuse alcohol. But, hepatitis B and C are also major causes of cirrhosis. Another cause is too much iron in the liver. This happens most often in the US in people with a hereditary disease called *hemochromatosis*, who absorb too much iron from their food.

Long-Term Exposure to Aflatoxin

This *carcinogenic* (cancer-causing) substance is produced in tropical and subtropical regions by a fungus that often contaminates peanuts, wheat, soybeans, ground nuts, corn, and rice.

Vinyl Chloride and Thorium Dioxide (Thorotrast)

These chemicals are risk factors for angiosarcoma of the liver (See "What is Liver Cancer?"). They also increase the risk of developing cholangiocarcinoma and hepatocellular cancer, but to a far lesser degree. These cancer-causing chemicals have become much less important since Thorotrast is no longer used and exposure of workers to vinyl chloride is strictly regulated.

Birth Control Pills

The section "What is Liver Cancer?" mentioned birth control pills, also known as oral contraceptives as a cause of benign tumors called hepatic adenomas. Oral contraceptives may also slightly increase the risk of hepatocellular cancer. Most of the studies linking oral contraceptives and hepatocellular cancer involve types of oral contraceptives that are no longer used. Current oral contraceptives use different types of estrogens, different estrogen doses, and different combinations of estrogens with other hormones. It is not known if the newer oral contraceptives significantly increase hepatocellular cancer risk.

Anabolic Steroids

Anabolic steroids are male hormones that are used by some athletes to increase their strength. Long-term anabolic steroid use can slightly increase the risk of hepatocellular cancer. Cortisone-like steroids, such as dexamethasone, do not carry this same risk.

Arsenic

Drinking water contaminated with arsenic increases the risk of hepatocellular cancer in some parts of the world.

Do We Know What Causes Liver Cancer?

Although we know about several risk factors for hepatocellular cancer, the exact way in which these factors cause normal liver cells to become cancerous is only partially understood. Scientists believe that cancers develop in two steps. The first step is damage to the DNA of the cells. DNA contains the instructions for nearly every chemical process in our bodies. Some of these instructions help cells to grow at a proper rate. If these instructions are altered, the cells may grow out of control and form a tumor. Fortunately, our cells have the ability to repair our DNA, so most DNA damage does not cause cancer.

Certain chemicals that cause liver cancer, such as aflatoxins, are known to damage the DNA in liver cells. Recent studies have shown that aflatoxins can damage the p53 gene, which normally works to prevent cells from growing too much. Damage to p53 DNA can lead to increased growth of abnormal cells and formation of cancers.

Infection of liver cells with hepatitis viruses can also cause DNA damage. These viruses have their own DNA, which carries instructions on how to infect cells and produce more viruses. In some patients this viral DNA can insert itself into a liver cell's DNA. But scientists still don't know exactly how this leads to cancer.

Although scientists are beginning to understand this process, much more must be learned. It is hoped that a more complete understanding will help develop ways to better prevent and treat liver cancers.

Can Liver Cancer Be Prevented?

Most liver cancers can be prevented by public health measures that reduce exposure to known risk factors for this disease.

Worldwide, the most significant risk factor is infection with hepatitis B virus (HBV) and hepatitis C virus (HCV). A recently developed vaccine can prevent hepatitis B infection. All children should be vaccinated to prevent this infection and to reduce the risk of liver cancer and liver damage from hepatitis.

There is no vaccine for hepatitis C. Therefore, preventing HCV infection and HBV infection in people who have not been immunized is based on understanding the ways these viruses spread. These viruses are spread through blood transfusions, by contaminated needles of intravenous drug abusers, and by unprotected sexual intercourse. Also, mothers who are hepatitis virus carriers can pass the virus to their children at birth or in early infancy. Blood banks in the United States routinely perform tests to identify donated blood infected with these viruses. All infected blood is discarded.

Recent studies indicate that a new treatment for these infections called interferon can lower a patient's risk of developing liver cancer.

Prevention of liver cancers associated with cirrhosis caused by alcohol abuse remains a challenge.

Changing the way certain grains are stored in tropical and subtropical countries could reduce exposure to cancer-causing substances such as aflatoxins. Many industrialized countries already have regulations to prevent and monitor grain contamination.

Better anti-parasite therapies and improved access to health information and health care can decrease the risk of liver cancers in countries where *Clonorchis sinensis* (liver fluke) infections are a significant cause of cholangiocarcinoma.

Most industrialized countries have regulations to protect consumers and workers from *carcinogens* (cancer-causing chemicals). These regulations have essentially eliminated certain chemicals as a cause of liver cancer.

Certain inherited diseases can cause cirrhosis of the liver, increasing the risk of liver cancer. Finding and treating these diseases early could lower this risk.

Can Liver Cancer Be Found Early?

Because signs and symptoms do not usually appear until the cancer is in its later stages, liver cancer is seldom diagnosed early. Also, no screening tests are sensitive enough for routine use. Small liver tumors are hard to detect by physical examination because most of the liver is covered by the right rib cage. Liver cancers tend to grow fast. The most common type of primary liver cancer, hepatocellular carcinoma, doubles in size every four months.

Liver cancers can sometimes be diagnosed using a blood test for *alpha-fetoprotein* (AFP). AFP is a protein that is normally present in high concentrations in the blood of fetuses but disappears shortly after birth. If it is found in the blood of adults it suggests they may have a liver cancer.

Tests for AFP have been used to look for early tumors in people at high risk for liver cancer. Unfortunately, some tumors do not produce much of this protein. Often by the time AFP is elevated, the tumor is too large to be removed or it has spread outside the liver. Some noncancerous liver diseases can also raise AFP levels. In areas where hepatocellular cancer is very common, use of the AFP blood test for hepatocellular cancer screening has resulted in the detection of many tumors at an earlier stage.

Many patients who develop liver cancer have long-standing *cirrhosis* (scar tissue formation due to liver cell damage). If a patient with cirrhosis gets worse for no apparent reason, doctors should suspect that liver cancer may be the cause, and do appropriate tests.

Ultrasonography (ultrasound) is a test that uses sound waves to create pictures of internal organs such as the liver. Some doctors recommend using this test in people with certain hepatocellular cancer risk factors to help find cancers earlier.

How Is Liver Cancer Diagnosed?

Signs and Symptoms of Liver Cancer

Although signs and symptoms are usually not present until the late stages of liver cancer, sometimes they may show up early and lead to an early diagnosis. Many signs and symptoms of liver cancer are relatively nonspecific. They can be caused by other cancers or by noncancerous diseases. Still, if you have any of the following problems, see a doctor right away:

- Unexplained weight loss
- *Anorexia* (persistent lack of appetite)
- *Early satiety* (feeling very full after a small meal)
- Persistent abdominal pain
- Increasing abdominal swelling
- Jaundice (yellow-green coloration of the skin and eyes)
- Deterioration in your condition if you have chronic hepatitis or cirrhosis
- Liver enlargement or a mass that can be felt in the area of the liver

Some liver tumors produce hormones that act on organs other than the liver. These hormones may cause *hypercalcemia* (high blood calcium levels), *hypoglycemia* (low blood sugar levels), or enlargement of the breasts in men. High calcium levels can lead to weakness and low blood sugar levels can cause fainting and even coma. These unusual findings may cause doctors to suspect a disease of the nervous system or an *endocrine* (hormone-producing) gland, rather than a liver cancer.

If you have one or more of these symptoms, doctors will use one or more methods to find out if the disease is really present.

History and Physical Examination

The doctor will take your complete medical history (medical interview) to check for risk factors and symptoms. Then the doctor will examine you to look for signs of liver cancer and other health problems.

Imaging Tests

Ultrasonography (ultrasound): Ultrasound uses sound waves and their echoes to produce a picture of internal organs such as the liver. A little microphone-like instrument called a *transducer* emits sound waves. These waves bounce off internal organs and the transducer also detects these echoes. A computer processes these echoes into a detailed image. The echoes produced by most liver tumors differ from those of normal liver tissue. Different echo patterns can help distinguish some types of liver tumors from one another.

This is a very easy procedure. It uses no radiation, which is why it is routinely used in pregnant women to look at developing fetuses. When you undergo an ultrasound examination, you simply lie on a table and a technician moves the transducer over the skin overlying the part of your body being examined. Usually, the skin is first lubricated with oil or ultrasound gel.

Computed tomography (CT): The CT scan is an x-ray procedure that produces detailed cross-sectional images of your body. Instead of taking one picture as does a conventional x-ray, a CT scanner takes many pictures as it rotates around you. A computer then combines these pictures into an image of a slice of your body. The machine will take pictures of multiple slices of the part of your body that is being studied. This test is very useful in identifying many types of liver tumors. Often after the first set of pictures is taken you will receive an intravenous injection of a "dye" or *radiocontrast agent* that helps better outline structures in your body. A second set of pictures will then be taken. The injection can also cause some flushing. Some people are allergic and get hives or rarely more serious reactions like trouble breathing and low blood pressure. Be sure to tell the doctor if you have ever had a reaction to any contrast material used for x-rays.

CT scans take longer than regular x-rays and you need to lie still on a table while they are being done. But just like other computerized devices, they are getting faster and your stay might be pleasantly short. Also, you might feel a bit confined by the machine you have to lie in while the pictures are being taken.

Magnetic resonance imaging (MRI): MRI scans use radio waves and strong magnets instead of x-rays. The energy from the radio waves is absorbed and then released in a pattern formed by the type of tissue and by certain diseases. A computer translates the pattern of radio waves given off by the tissues into a very detailed image of parts of the body. A contrast material might be injected just as with CT scans. MRI scans are very helpful in looking at liver cancers. Sometimes they can tell a benign tumor from a malignant one.

MRI scans may be a little more uncomfortable than CT scans. First, they take longer -- often up to an hour. Also, you may be placed inside a tube, which is confining and can upset people with claustrophobia. Finally, the machine gives off a thumping noise that you may find disturbing. Some places will provide headphones with music to block this out. However, the benefit of the test outweighs any discomfort of the test.

Other Procedures

Angiography: *Angiography* is an x-ray procedure for examining blood vessels. *Contrast medium* is injected into an artery before x-ray images are taken. The contrast medium outlines the blood vessels on x-ray pictures. Angiography is useful in showing the arteries that supply blood to a liver cancer. This information can help surgeons decide whether a cancer can be removed and if so, provides help in planning the operation. *Digital subtraction angiography* uses computers to produce more detailed images of blood vessels. *Dynamic sequential CT scanning* combines CT scanning and angiography. It is not routinely used but is sometimes helpful in planning surgery.

This can be an uncomfortable procedure because the radiologist who performs the procedure has to put a tiny catheter into the artery leading to your liver. Usually the catheter is put into an artery in your groin and threaded up into the liver artery. Then the dye is injected quickly to outline all the vessels while the x-rays are being taken. Usually, a local anesthetic is used.

Laparoscopy: This procedure uses a thin, lighted tube through which a doctor can view the liver and other internal organs. The tube is inserted through a small incision in the front of the abdomen. Laparoscopy provides a view of organs, which can help in planning surgery or other treatments. Also, doctors can manipulate small instruments through this tube to remove small tissue samples to examine under the microscope.

Laparoscopy is usually performed at an outpatient center but it is like an operation. You will be sedated and put to sleep just as for any operation. Because the surgeon only makes a small incision to insert the tubes, you will not feel much pain after surgery. You should be able to go home after you recover from the anesthesia.

Biopsy: Although imaging tests such as ultrasonography, CT and MRI scans, and angiography can suggest that a liver cancer is present, the only way to be certain is to take a *biopsy* (sample of the tumor tissue) and examine it under a microscope.

There are several biopsy methods that are used to take samples of liver tissue. An *incisional biopsy* (removing a piece of the tumor) or an *excisional biopsy* (removing the entire tumor with a margin of surrounding *benign*, noncancerous, liver tissue) can be done during a surgical operation. However, since doctors usually prefer to know the exact type of tumor before surgery, other types of biopsy methods are often used.

If the tumor is very large or has spread throughout the liver, a needle can be placed anywhere into the liver and tumor cells sucked into the needle with a syringe. If the tumor is smaller, the doctor will use ultrasonography or CT scanning to guide the needle. With this approach, the doctor slowly advances the needle while its position is checked by one of these imaging tests. When the images show that the needle is in the tumor, a sample is removed and sent to the lab to be looked at under a microscope.

When this is done, the skin where the needle is placed will be deadened with local anesthesia. The only hard part of this procedure is lying still while the needle is advanced.

Biopsy specimens can also be taken during laparoscopy. This allows the doctor to see the surface of the liver and take samples of abnormal appearing areas.

Alpha-fetoprotein (AFP) blood test: AFP levels in your blood will be checked if the doctor thinks you have liver cancer because they are increased in most patients with hepatocellular carcinoma. AFP levels are not abnormally high with other types of primary liver cancer (cholangiocarcinoma, angiosarcoma, etc.). Comparing AFP levels of blood samples taken before and after treatment can show how completely the cancer has been removed or destroyed or if it is coming back.

Other blood tests: Because liver cancer often arises in damaged livers, doctors need to know the condition of your liver before proceeding with treatment. A series of tests can be done on your blood. These tests can evaluate the condition of your liver tissue not affected by the cancer. Since the doctor will need to remove a good part of your liver, you may not be able to have curative surgery if your liver is not healthy.

How Is Liver Cancer Staged?

Staging is the process of finding out how widespread a cancer is. The stage of a liver cancer is the most important factor in considering treatment options. A *staging system* is a standardized way for the cancer care team to summarize information about how far a cancer has spread.

The American Joint Committee on Cancer (AJCC) TNM System

The most common system used to describe the stages of liver cancers is the *American Joint Committee on Cancer (AJCC) TNM system*. **T** stands for tumor (its size and how far it has spread within the liver and to nearby organs). **N** stands for spread to lymph nodes (bean-sized collections of immune system cells that help fight infections and cancers). **M** is for *metastasis* (spread to distant organs). Using the TNM staging system, information about the tumor, lymph nodes, and metastasis is combined to assign a stage. This process is called stage grouping. The stage is described in Roman numerals from I to IV.

Summary of AJCC Stages

Stage I:

- The tumor is less than 1 inch in diameter and does not invade blood vessels.

Stage II:

- There is a single tumor less than 1 inch in diameter that does invade blood vessels; *or*
- There is single tumor larger than 1 inch that does not invade blood vessels; *or*
- There are several tumors less than 1 inch in only one lobe of the liver and they do not invade blood vessels.

Stage IIIA:

- There is a single tumor larger than 1 inch in diameter that does invade blood vessels *or*,
- There are several tumors in one lobe and at least one is larger than 1 inch and they do invade blood vessels *or*,
- There are several tumors less than 1 inch in only one lobe of the liver that do invade blood vessels.

Stage IIIB:

Any tumor stages I -III but the cancer has also spread to lymph nodes.

Stage IV:

- There are multiple tumors in more than one lobe of the liver *or*,
- The cancer has spread to other parts of the body.

Localized Resectable, Localized Unresectable and Advanced Liver Cancer

These categories help surgeons decide if your liver cancer might be cured by surgery. Your liver cancer might be curable by surgery only if it is in stages I, II, or IIIA, and if the non-cancer part of your liver is healthy. Doctors often classify these liver cancers as *localized resectable*. Resectable is the medical term meaning "able to be removed by surgery."

Cancers that have not spread beyond the liver but cannot be completely removed by surgery are classified as *localized unresectable*. There are several reasons why it might not be possible to safely remove a localized liver cancer. If the noncancerous part of your liver is not healthy (due to cirrhosis, for example), surgery might not leave enough liver tissue behind for it to function properly. Also, curative surgery may not be possible if your cancer is close to the area where the liver meets the main arteries, veins, and bile ducts.

Cancers that have spread throughout most of the liver and/or have spread to other organs are classified as *advanced*.

Detailed Information on AJCC Liver Cancer Stages

The following information on exactly how doctors determine the grouped stage (I, II, III, and IV) of liver cancers is included for patients who are interested in understanding these rather technical details. However, if your doctor has already told you the grouped stage of your cancer, you can skip this section and start at the beginning of the treatment section.

T categories of liver cancer:

- TX: Primary tumor cannot be assessed (due to incomplete information)
- T0: No evidence of primary tumor
- T1: Single area of tumor 2.0 cm (about 3/4 inch) or smaller without invasion of blood vessels
- T2: Tumors have one of the following combinations of features:
 - Single area of tumor 2.0 cm or smaller with blood vessel invasion,
 - Multiple tumors limited to one lobe (left or right side of the liver), none larger than 2.0 cm without blood vessel invasion,
 - A single tumor larger than 2.0 cm without blood vessel invasion.
- T3: Tumors have one of the following combinations of features:
 - Single area of tumor larger than 2.0 cm with blood vessel invasion,
 - Multiple tumors limited to one lobe, none larger than 2.0 cm, with vascular invasion,
 - Multiple tumors limited to one lobe, any of which is larger than 2.0 cm, with or without blood vessel invasion.
- T4: Tumors have one of the following features:
 - Multiple tumors in more than one lobe
 - Tumor(s) involving a major branch of portal or hepatic vein(s)
 - Spread to organs near the liver (other than the gallbladder)
 - Spread to the peritoneum (thin membrane that covers organs of the abdomen)

N categories of liver cancer:

- NX: Regional (near the liver) lymph node spread cannot be assessed (due to incomplete information)
- N0: No regional lymph node spread
- N1: Regional lymph node spread

M categories of liver cancer:

- MX: Presence of distant metastasis (spread to lymph nodes not near to the liver, or to other organs such as the lungs or bones) cannot be assessed due to incomplete information.
- M0: No distant metastasis
- M1: Distant metastasis

AJCC stage groupings:

Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage IIIA	T3, N0, M0
Stage IIIB	T1, N1, M0 T2, N1, M0 T3, N1, M0
Stage IVA	T4, any N, M0
Stage IVB	any T, any N, M1

As an example of the staging process, consider a patient with multiple tumors, none of which are larger than 3/4 inch, that are all located in the left lobe of the liver. The cancer has spread to lymph nodes near the liver but not to other lymph nodes. It has not spread to the lungs, bones, or other organs. This is a T2, N1, M0 cancer. Using the stage grouping information in this section, this is described as a stage IIIB cancer.

How Is Liver Cancer Treated?

This information represents the views of the doctors and nurses serving on the American Cancer Society's Cancer Information Database Editorial Board. These views are based on their interpretation of liver cancer treatment studies published in medical journals, as well as their own professional experience. The treatment information in this document is not, however, official policy of the Society and is not intended as medical advice to replace the expertise and judgment of your cancer care team. It is intended to help you and your family make informed decisions, together with your cancer care team. Don't hesitate to ask them questions about your treatment options. In addition to the information in this document, we encourage interested patients to seek out treatment information from other reliable sources.

After liver cancer is diagnosed and staged, the cancer care team can recommend one or more treatment options. Choosing a treatment plan is a major decision, so it is important to take time and think about all of the choices.

In creating your treatment plan, the most important factor to consider is the stage (extent) of the cancer. But you and your cancer care team will also take into account your age, general state of health, and personal preferences.

It is often a good idea to seek a second opinion, especially with doctors experienced in treating liver cancer. A second opinion can provide more information and help you feel more confident about the treatment plan that is being considered. Some insurance companies require a second opinion before they will agree to pay for certain treatments. Most companies will pay for the second opinion.

The three main methods of cancer treatment are surgery, chemotherapy, and radiation therapy. Sometimes the best treatment approach uses two or more of these methods. Your recovery is the goal of your cancer care team. If a cure is not possible, the goal may be to remove or destroy as much of the cancer as possible to prevent the tumor from growing, spreading, or returning for as long as possible. Sometimes treatment is aimed at relieving symptoms. This is called *palliative* treatment.

Surgical Resection

Resection (removal of the tumor) offers the only chance to cure a liver cancer. If you can withstand removal of all cancer visible to the surgeon at the time of the operation you will have the best outlook for survival. Unfortunately, complete removal of most liver cancers is not possible. Often the cancer has spread beyond the liver or has become quite large or may be present in too many different parts of the liver. Your ability to withstand liver surgery also depends on the health of your noncancerous liver tissue. About 30% of hepatocellular carcinoma patients in the United States have cirrhosis. If you have severe cirrhosis, the removal of even a small amount of liver tissue at the edges of your cancer might not leave enough liver tissue to perform essential functions. If you have cirrhosis you would be considered eligible for surgery only if your cancer is small.

Liver Transplantation

Although total hepatectomy (removing the entire liver) and liver transplantation are rarely used to treat liver cancer, studies are in progress to determine which liver cancer patients are most likely to benefit from this treatment. Advances in transplantation immunology are expected to reduce the risk of liver rejection and the severity of side effects caused by anti-rejection drugs that suppress the patient's immune system. Increased public awareness about the importance of organ donation is an essential public health goal that could make this treatment available to more patients with liver cancer and other serious liver diseases.

Tumor Ablation or Embolization

Ablation refers to local (rather than systemic) methods that destroy the tumor without removing it. One new approach, called *radiofrequency ablation*, uses high-energy radio waves for treatment. A thin, needle-like probe temporarily placed into the tumor releases these radio waves. Placement of the probe is accurately guided by CT scans. The probe releases high frequency alternating current that creates frictional heating and destroys the cancer cells. Other examples of methods for liver tumor ablation include *cryosurgery* (destruction of tumor by freezing it with a very cold metal probe) and *ethanol ablation* (injecting concentrated alcohol directly into the tumor to kill cancer cells). Since these three treatments do not require surgery to remove any of the patient's liver tissue, they are excellent options for patients whose disease is not curable with surgery.

The blood supply to the cancer can be reduced by surgically tying the artery that feeds the cancer or by *embolization* (injecting materials that plug up the artery). However, these treatments also reduce blood supply to the normal liver tissue. This may be very dangerous for patients with diseases such as hepatitis and cirrhosis that are affecting their noncancerous liver tissue. Many times the embolization is combined with chemotherapy. This combination treatment is known as *chemoembolization*.

Chemotherapy

Systemic chemotherapy uses anticancer drugs that are injected into a vein or given by mouth. These drugs enter the bloodstream and reach all areas of the body, making this treatment potentially useful for cancers that have *metastasized* (spread) to distant organs.

Chemotherapy drugs kill cancer cells but also damage some normal cells, which can lead to side effects.

The side effects of chemotherapy depend on the types of drugs, the amount taken, and the length of treatments. Temporary side effects of chemotherapy might include nausea and vomiting, loss of appetite, loss of hair, and mouth sores. Because chemotherapy can damage the blood-producing cells of the bone marrow, the blood cell counts might become low. This can result in an increased chance of infection (due to a shortage of white blood cells), bleeding or bruising after minor cuts or injuries (due to a shortage of blood platelets), and shortness of breath (due to low red blood cell counts). Fatigue is also quite common and may be caused by low red blood counts, by other reasons related to the chemotherapy, or the cancer itself.

Most side effects disappear once treatment is stopped. Hair will grow back after treatment ends. Anyone who has problems with side effects should talk with their cancer care team. There are remedies for many of the temporary side effects of chemotherapy. For example, *antiemetic* (antinausea) drugs to prevent or reduce nausea and vomiting can be given. Other drugs called growth factors can be given to help the bone marrow recover after chemotherapy.

Hepatocellular cancer resists most chemotherapy drugs. The only drugs that have been effective in shrinking the tumors are doxorubicin, which is the most successful single drug, and cisplatin. In most studies, systemic chemotherapy has not helped patients to live longer.

Radiation therapy

Radiation therapy uses high-energy rays to kill cancer cells. *External beam radiation therapy* focuses radiation delivered from outside the body on the cancer. With liver cancer, this type of radiation therapy can be used to shrink the cancer to palliate symptoms such as pain. It does not improve survival. Although liver cancer cells are sensitive to the radiation, this treatment can't be used at very high doses because the radiation also kills normal liver tissue.

Three-dimensional conformal radiation therapy is a new form of external beam radiation therapy that uses sophisticated computers to precisely map the location of a tumor. You are then fitted with a plastic mold resembling a body cast to keep you still so that the radiation can be aimed more accurately. Radiation beams are then aimed at the tumor from several directions. By aiming the radiation more accurately, doctors can reduce radiation damage to normal liver tissue.

[Level 3] Clinical Trials

[Level 4] The purpose of clinical trials: Studies of promising new or experimental treatments in patients are known as clinical trials. A clinical trial is only done when there is some reason to believe that the treatment being studied may be valuable to the patient. Treatments used in clinical trials are often found to have real benefits. Researchers conduct studies of new treatments to answer the following questions:

- Is the treatment helpful?
- How does this new type of treatment work?
- Does it work better than other treatments already available?
- What side effects does the treatment cause?
- Are the side effects greater or less than the standard treatment?
- Do the benefits outweigh the side effects?
- In which patients is the treatment most likely to be helpful?

[Level 4] Types of clinical trials: There are three phases of clinical trials in which a treatment is studied before it is eligible for approval by the FDA (Food and Drug Administration).

[Level 4] Phase I clinical trials: The purpose of a Phase I study is to find the best way to give a new treatment and how much of it can be given safely. Physicians watch patients carefully for any harmful side effects. The treatment has been well tested in laboratory and animal studies, but the side effects in patients are not completely known. Doctors conducting the clinical trial will start by giving very low doses of the drug to the first patients and increasing the dose for later groups of patients until side effects appear. Although doctors are hoping to help patients, the main purpose of a phase I study is to test the safety of the drug.

[Level 4] Phase II clinical trials: These are designed to see if the drug works. Patients are given the highest dose that doesn't cause severe side effects (determined from the phase I study) and closely observed for an effect on the cancer. The doctors will also look for side effects.

[Level 4] Phase III clinical trials: These Phase III studies involve large numbers of patients. Some clinical trials may enroll thousands of patients. One group (the control group) will receive the standard (most accepted) treatment. The other groups will receive the new treatment. Usually doctors study only 1 new treatment to see if it works better than the standard treatment, but sometimes they will test 2 or 3. All patients in Phase III studies are closely watched. The study will be stopped if the side effects of the new treatment are too severe or if one group has had much better result than the others.

If you are in a clinical trial, you will receive excellent care. You will have a team of experts looking at you and monitoring your progress very carefully. The study is especially designed to pay close attention to you.

However, there are some risks. No one involved in the study knows in advance whether the treatment will work or exactly what side effects will occur. That is what the study is designed to discover. While most side effects will disappear in time, some can be permanent or even life threatening. Keep in mind, though, that even standard treatments have side effects. Depending on many factors, you may decide to enroll in a clinical trial.

[Level 4] Deciding to enter a clinical trial: Enrollment in any clinical trial is completely up to you. Your doctors and nurses will explain the study to you in detail and will give you a form to read and sign indicating your desire to take part. This process is known as giving your informed consent. Even after signing the form and after the clinical trial begins, you are free to leave the study at any time, for any reason. Taking part in the study will not prevent you from getting other medical care you may need.

To find out more about clinical trials, ask your cancer care team. Among the questions you should ask are:

- What is the purpose of the study?
- What kinds of tests and treatments does the study involve?
- What does this treatment do?
- What is likely to happen in my case with, or without, this new research treatment?
- What are my other choices and their advantages and disadvantages?
- How could the study affect my daily life?
- What side effects can I expect from the study? Can the side effects be controlled?
- Will I have to be hospitalized? If so, how often and for how long?
- Will the study cost me anything? Will any of the treatment be free?
- If I am harmed as a result of the research, what treatment would I be entitled to?
- What type of long-term follow-up care is part of the study?
- Has the treatment been used to treat other types of cancers?

You can get a list of current clinical trials by calling the National Cancer Institute's Cancer Information Service toll free at 1-800-4-CANCER or visiting the NCI clinical trials Web sites for patients [[Link to cancertrials.nci.nih.gov](http://cancertrials.nci.nih.gov)] or health care professionals [[Link to cancernet.nci.nih.gov/prot/protsrch.shtml](http://cancernet.nci.nih.gov/prot/protsrch.shtml)].

Treatment of Liver Cancer by Stage

Although the AJCC (TNM) staging system is often used for precisely describing the extent of spread of a liver cancer, a simpler system is more practical for use in selecting treatment options. This system divides liver cancers into one of three categories - localized resectable, localized unresectable, and advanced.

Localized Resectable: If your cancer is stage I, II or III and your noncancerous liver tissue is healthy, surgery may cure you. Only a small number of people with liver cancer fall into this category. If you were to have curative surgery, your 3-year survival rate would be about 50%. You would probably not be helped by *adjuvant* (additional) treatment with chemotherapy although clinical trials are still studying this approach with new drugs.

Localized Unresectable: If your cancer is too large, there are too many tumors to be removed, or the rest of your liver is unhealthy, you fall into this category. Your doctors may recommend cryosurgery or injection of alcohol into the cancers. Another option is embolization with or without chemotherapy. These treatments are all palliative. They are intended to reduce any symptoms you might have. It is not known whether they can prolong your life. You also might want to participate in a clinical trial.

Some patients may choose to have a liver transplant, particularly if they have fibrolamellar hepatocellular cancer, which is a very favorable type. Transplantation is also considered for patients with small cancers, who cannot undergo a surgical resection because they have cirrhosis. This is a very serious operation where your liver is removed and replaced with one from a donor who has just died. Although this is a very difficult operation, it has helped some people.

The opportunities for liver transplantation are limited. Not many livers are available for cancer patients because they are generally used for more curable diseases. Also, people needing a transplant must wait until a liver is available and usually that takes too long a time for most people with liver cancer.

New approaches to radiation therapy are being tried, using *radiosensitizers* (drugs that make cancers more vulnerable to radiation). Combinations of surgery, chemotherapy, and external beam radiation therapy are being studied to see if they are useful. For example, chemotherapy is being studied as a way to lower the risk of distant recurrence after liver transplantation.

If you have localized unresectable hepatocellular cancer your expected 3-year survival rate is about 20%, depending on your general health, the health of your liver, and your exact stage.

Advanced: This means your cancer has spread outside your liver. There is no standard treatment for this stage of hepatocellular cancer. As with localized resectable hepatocellular cancer, clinical trials of new approaches to chemotherapy (new drugs and regional chemotherapy), new forms of radiation therapy (with radiosensitizers or targeting via antibodies), and other new treatments (immunotherapy and gene therapy) may help you. These clinical trials are also important for improving the outlook for future patients. The 3-year survival rate for people with advanced hepatocellular cancer is less than 15%. Even though treatments such as radiation or chemotherapy cannot prolong your life, they may help relieve pain and other symptoms. Do not hesitate to discuss any symptoms with your cancer care team.

Complementary and Alternative Methods

If you are considering using any unproven alternative or complementary treatments, it is best to discuss this openly with your cancer care team and request information from the American Cancer Society or the National Cancer Institute. Some unproven treatments can interfere with standard medical treatments or may cause serious side effects.

What Should You Ask Your Doctor About Liver Cancer?

It is important to have honest, open discussions with your cancer care team. Consider these questions:

- What kind of liver cancer do I have? (There are different types of liver cancer. Also, there are certain subtypes of hepatocellular carcinoma such as the "fibrolamellar" variety that carry a better prognosis than others.)
- Has my cancer spread beyond the liver?
- Can the stage of my cancer be determined and what does that mean.
- What treatment choices do I have?
- What do you recommend and why?
- What risks or side effects are there to the treatments you suggest?
- What are the chances my cancer will recur with these treatment plans?
- What should I do to be ready for treatment?
- Based on what you've learned about my cancer, what is my prognosis?

In addition to these sample questions, be sure to write down some of your own. For instance, you may want to ask about second opinions or about clinical trials for which you may qualify.

What Happens After Treatment For Liver Cancer?

Follow-Up Tests

Your doctor may order imaging tests such as ultrasound or abdominal CT scans to watch for a recurrence or a new tumor. If your alpha-fetoprotein (AFP) levels were elevated, this blood test may be repeated at regular intervals. If surgery was curative, levels of AFP should have returned to within the normal range.

New Symptoms

It is important for you to report any new symptoms right away, so that cancer recurrence or side effects of therapy can be treated as effectively as possible.

The doctors, nurses, oncology social workers, and other members of the health care team can help refer you to other organizations for help. We have information and programs to meet your medical, emotional, social, and financial needs. Some of these are listed in the section "Additional Resources."

Other Things to Consider

During and after treatment you may be able to hasten your recovery and improve your quality of life by taking an active role. Learn about the benefits and disadvantages of each of your treatment options, and ask questions of your cancer care team if there is anything you do not understand. Learn about and look out for side effects of treatment, and report these promptly to your cancer care team so that they can take steps to minimize them and shorten their duration.

Remember that your body is as unique as your personality and your fingerprints. Although understanding your cancer's stage and learning about the effectiveness of your treatment options can help predict what health problems you may face, no one can say precisely how you will respond to cancer or its treatment.

You may have special strengths such as a history of excellent nutrition and physical activity, a strong family support system, or a deep faith, and these strengths may make a difference in how you respond to cancer. In fact, behavioral scientists have recently found that some people who took advantage of a social support system, such as a cancer support group, had a better quality of life. There are also experienced professionals in mental health services, social work services and pastoral services who may help you cope with your illness.

If you are being treated for cancer, be aware of the battle that is going on in your body. Radiation therapy and chemotherapy add to the fatigue caused by the disease itself. Rest as much as you need to so that you will feel better as time goes on. Exercise once you feel rested enough. Ask your cancer care team whether your cancer or its treatments might limit your exercise program or other activities.

A cancer diagnosis and its treatment are major life challenges, with an affect on you and everyone who cares for you. Before you get to the point where you feel overwhelmed, consider attending a meeting of a local support group. There are many groups available that provide emotional support, friendship, and understanding. Your health care team can suggest other organizations that might help you during your recovery from treatment. If you need individual assistance in other ways, contact your hospital's social service department or call us (1-800-ACS 2345) for help in contacting counselors or other services.

What's New In Liver Cancer Research And Treatment?

There is always research going on in the area of liver cancer. Scientists are looking for causes and ways to prevent liver cancer and doctors are working to improve treatments.

Prevention

Researchers are studying ways to prevent or treat hepatitis infections before they cause liver cancers. Progress is being made in treating chronic hepatitis with drugs that boost the patient's immune system. Some scientists believe that vaccinations and improved treatments for hepatitis could prevent about half of liver cancer cases worldwide.

Chemotherapy

New forms of systemic and regional chemotherapy combined with other treatments are being tested in clinical trials.

Gene Therapy

Scientists are learning more about many of the genes that are damaged when normal liver cells change to hepatocellular cancer in hopes of developing *gene therapies* aimed at replacing these defective DNA sequences. The p53 gene is a tumor suppressor gene that is often altered in liver cancers. In normal liver cells, it prevents excessive growth, helps cells repair damage to their DNA, and promotes the death of cells with DNA damage too extensive to be repaired. Restoring normal p53 DNA to liver cancer cells might suppress tumor growth and cause the cancer cells to die. Clinical trials are in progress to study the feasibility of this type of therapy, the toxicity and, of course, short and long-term results.

Additional Resources

National Organizations and Web sites

The following organizations can provide additional information and resources.*

**Inclusion on this list does not imply endorsement by the American Cancer Society*

American Liver Foundation
Telephone: 1-800-GO-LIVER (465-4837)
Internet Address: www.liverfoundation.org

National Cancer Institute
Telephone: 1-800-4-CANCER
Internet Address: www.nci.nih.gov (NCI home page)

American Cancer Society Information

After Diagnosis: A Guide for Patients and Families (Booklet; Code #9440)

Caregiving: A Step-By-Step Resource for Caring for the Person with Cancer at Home (Book; Code #9422)

Caring for the Patient with Cancer at Home (Booklet; Code# 4656)

Other Publications*

**Inclusion on this list does not imply endorsement by the American Cancer Society*

A Cancer Survivor's Almanac: Charting Your Journey. Edited by Barbara Hoffman, JD. National Coalition for Cancer Survivorship. Minnetonka, Minnesota: Chronimed Publishing, 1996.

Capossela Cappy, Warnock Sheila. *Share the Care: How to Organize a Group for Someone Who Is Seriously Ill.* New York: Simon and Schuster, 1995.

Dollinger Malin, Rosenbaum Ernest H. and Cable Greg. *Everyone's Guide to Cancer Therapy.* Kansas City, Missouri: Somerville House Books, 1997.

Morra Marion and Potts Eve. *Choices.* New York: Avon Books, 1994.

References

American Cancer Society. *Cancer Facts and Figures 2001.* Atlanta, Ga: American Cancer Society; 2001.

American Joint Committee on Cancer. *AJCC Cancer Staging Manual.* 5th ed. Philadelphia, Pa: Lippincott-Raven; 1997: 97-99.

Engstrom PF, Sigurdson E, Evans A. Primary Neoplasms of the Liver. In: Bast RC, Kufe DW, Pollock RE, Weischelbaum RR, Holland JF, Frei E, eds. *Cancer Medicine.* Hamilton, Ontario: BC Decker Inc.: 2000: 1391-1401

PDQ database. Adult primary liver cancer. Bethesda, Md: National Cancer Institute; 2000. Available at cancernet.nci.nih.gov/Cancer_Types/Liver_Cancer.shtml

Strauss, RM. Hepatocellular carcinoma, clinical, diagnostic and therapeutic aspects. In: Rustgi AK, ed. *Gastrointestinal Cancers.* Philadelphia, Pa: Lippincott-Raven; 1995: 479-496.

Watkins KT, Curley SA. Liver and Bile Ducts In: Abeloff MD, Armitage JO, Lichter AS, Niederhuber JE. *Clinical Oncology.* Philadelphia, PA. Churchill Livingstone: 2000: 1517-1544

Revised 4/26/01