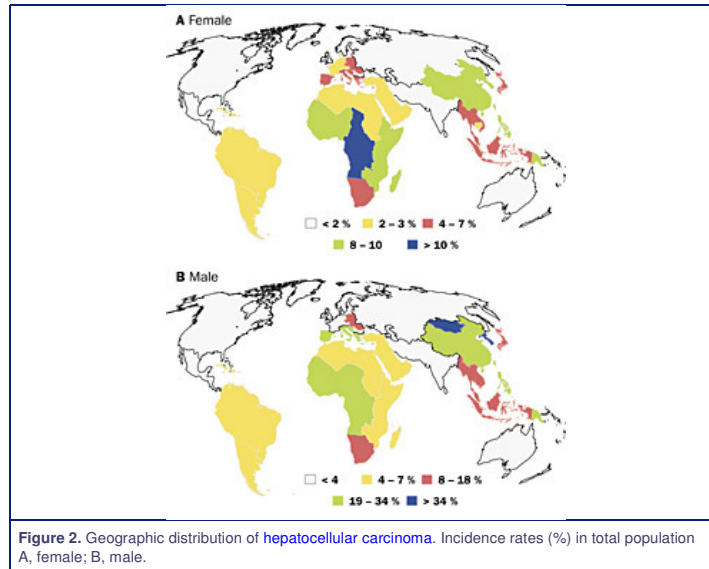


Hepatocellular Carcinoma (Liver Cancer): Introduction

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Hepatocellular carcinoma is a tumor of the liver. Hepatocellular carcinoma is responsible for over 12,000 deaths per year in the United States where the incidence of the disease is approximately 2.5 per 100,000 population. It is one of the most common malignancies in adults, and is more common in men than women (2-4:1), and blacks than whites. Worldwide, over a million deaths per year (about 10% of all deaths in the adult age range) can be attributed to hepatocellular carcinoma. The occurrence of hepatocellular carcinoma varies widely depending on geographic location. Whereas incidence in the Western world is less than two per 100,000 males, it is currently 40-60 per 100,000 in Africa and parts of the Far East. In the United States, hepatocellular carcinoma is more common in people of East Asian origin. In the future, the prevalence of hepatocellular carcinoma may increase in the United States and parts of Europe because of the high incidence of hepatitis C. At the same time, many experts expect incidence rates to decline in the Far East due to universal immunization for hepatitis B. Figure 2 illustrates the geographic distribution of hepatocellular carcinoma.



What is Hepatocellular Carcinoma?

Most primary liver cancers are classified as hepatocellular carcinoma. Hepatocellular carcinoma is a malignant tumor composed of cells resembling hepatocytes ; however, the resemblance varies with the degree of differentiation . Hepatocellular carcinoma is commonly associated with cirrhosis (Figure 3).

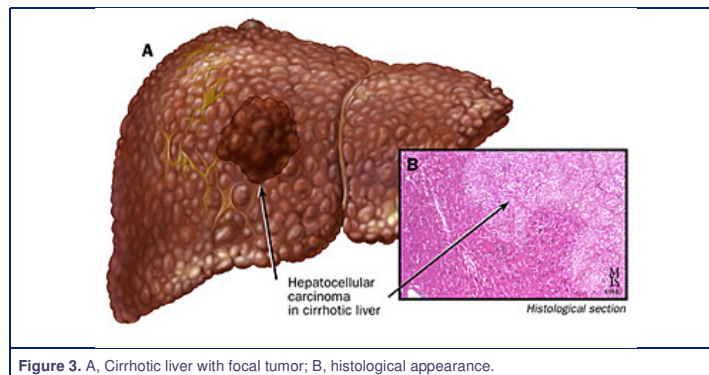


Figure 3. A, Cirrhotic liver with focal tumor; B, histological appearance.

This type of liver cancer is potentially curable by surgical resection. However, only those patients with localized disease are surgical candidates. Liver function impairment and degree of tumor localization determine patient prognosis proliferation . Clinical trials offer alternative treatment options for patients who are not candidates for resection.

Symptoms

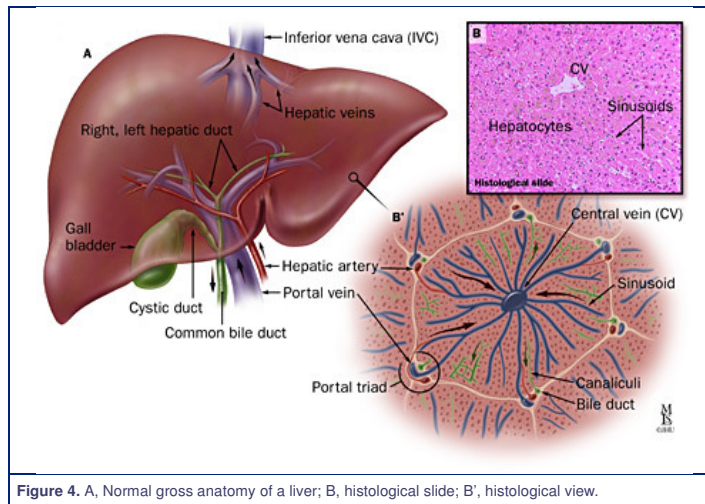
In the U.S., a significant number of hepatocellular carcinoma cases are detected during surveillance or investigation of underlying liver disease. Often, patients present with symptoms related to their underlying liver disease. In a report from Hong Kong, 76% of patients with hepatocellular carcinoma presented to their hepatoma clinic with abdominal distention or discomfort; less common presentations included weight loss (4.4%), gastrointestinal hemorrhage (4.4%), and jaundice (2.6%). In the Hong Kong series, only 2% were asymptomatic. Rarely, hepatocellular carcinoma can present as an acute abdomen resulting from spontaneous rupture of the tumor into the peritoneal cavity. Hepatocellular carcinoma should be considered in the differential diagnosis of hemorrhagic ascites.

Hepatocellular Carcinoma (Liver Cancer): Anatomy

Anatomy

The liver is the largest organ in the abdominal cavity and the most complex. It consists of a myriad of individual microscopic functional units call lobules. The liver performs a variety of functions including the removal of endogenous and exogenous materials from the blood, complex metabolic processes including bile production, carbohydrate homeostasis , lipid metabolism, urea formation, and immune functions.

The liver arises from the ventral mesogastrium and only the upper posterior surface is outside of that structure. The ligamentum teres and falciform ligament connect the liver to the anterior body wall. The lesser omentum connects it to the stomach and the coronary and triangular ligaments to the diaphragm. The liver is smooth and featureless on the diaphragmatic surface and presents with a series of indentations on the visceral surface where it meets the right kidney, adrenal gland, inferior vena cava, hepatoduodenal ligament and stomach (Figure 4).



The liver can be considered in terms of blood supply hepatocytes, Kupffer cells and biliary passages. The liver receives its blood supply from the portal vein and hepatic artery, the former providing about 75% of the total 1500 ml/min flow. Small branches from each vessel—the terminal portal venule and the terminal hepatic arteriole—enter each acinus at the portal triad. Pooled blood then flows through sinusoids between plates and hepatocytes in order to exchange nutrients. The hepatic vein carries efferent blood into the inferior vena cava and a supply of lymphatic vessels drains the liver.

Parenchymal cells or hepatocytes comprise the bulk of the organ and carry out complex metabolic processes. Hepatocytes are responsible for the liver's central role in metabolism (Figure 4B'). These cells are responsible for the formation and excretion of bile ; regulation of carbohydrate homeostasis ; lipid synthesis and secretion of plasma lipoproteins; control of cholesterol metabolism; and formation of urea, serum albumin, clotting factors, enzymes, and numerous proteins. The liver also aids in the metabolism and detoxification of drugs and other foreign substances.

Kupffer cells line the hepatic sinusoids and are part of the reticuloendothelial system, filtering out minute foreign particles, bacteria, and gut-derived toxins. They also play a role in immune processes that involve the liver.

Biliary passages begin as tiny bile canaliculi formed by hepatocytes. These microvilli-lined structures progress into ductules, interlobular bile ducts, and larger hepatic ducts. Outside the porta hepatis, the main hepatic duct joins the cystic duct from the gallbladder to form the common bile duct, which drains into the duodenum.

Hepatocellular Carcinoma (Liver Cancer): Causes

Hepatitis B and C

The two most important etiological factors contributing to hepatocellular carcinoma are hepatitis B and hepatitis C (Figure 5). In parts of China and Taiwan, 80% of hepatocellular carcinoma is due to hepatitis B. In the United States and Europe, hepatitis C and hepatitis B contribute equally to disease cases. In Japan, where the prevalence of hepatitis B and hepatitis C is similar, the incidence of hepatocellular carcinoma is higher in patients with hepatitis C compared to hepatitis B (10.4% vs. 3.9%). The pathogenesis of hepatocellular carcinoma in the presence of hepatitis B virus may be due to increased cell turnover from chronic liver disease, or a combination of processes specific to the hepatitis B virus. These may include integration of the hepatitis B DNA genome into the host genome, thereby disrupting the regulatory elements of cell cycling, or via transactivation of host oncogenes by either HBx protein or a truncated protein derived from pre-S2/S region of hepatitis B genome. The pathogenesis of hepatocellular carcinoma in hepatitis C is less understood. It is possible that some of these patients had previous exposure to hepatitis B virus.

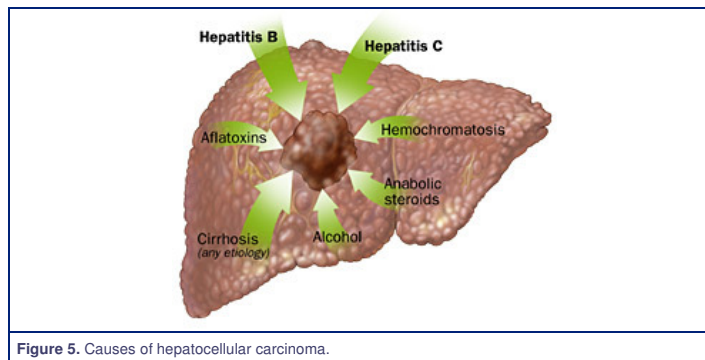


Figure 5. Causes of hepatocellular carcinoma.

Cirrhosis

Cirrhosis, irrespective of its etiology, is a risk factor for the development of hepatocellular carcinoma. The risk is 3–4 times higher in patients with cirrhosis compared to those with chronic hepatitis in a given population. An increase in hepatocellular proliferation may lead to the activation of oncogenes and mutation of tumor suppressor genes. These changes, in turn, may initiate hepatocarcinogenesis. In low-incidence areas, more than 90% of patients with hepatocellular carcinoma have underlying cirrhosis. However, the presence of cirrhosis is less (approximately 80%) in high-incidence areas, which is probably related to vertical transmission of hepatitis B virus in these areas (Figure 5).

Other Factors

Other etiological factors affecting disease incidence include aflatoxins, alcohol, hemochromatosis, and anabolic steroid use (Figure 5). Exposure to dietary carcinogenic aflatoxins, produced by *Aspergillus parasiticus* and *Aspergillus flavus*, is common in certain regions of Southeast Asia and sub-Saharan Africa. Hepatitis B is also common in these areas. The relative contribution of aflatoxins and the hepatitis B virus to the pathogenesis of hepatocellular carcinoma in these parts of the world are poorly understood. In patients with hepatitis C viral infection, alcohol has been found to be another contributing factor. Whether this is related to a more aggressive disease due to a combination of hepatitis C virus and alcohol, or whether alcohol is an independent factor remains unknown. The incidence of hepatocellular carcinoma in patients with hemochromatosis can be as high as 45%, and often the tumor is multifocal.

Hepatocellular Carcinoma (Liver Cancer): Diagnosis

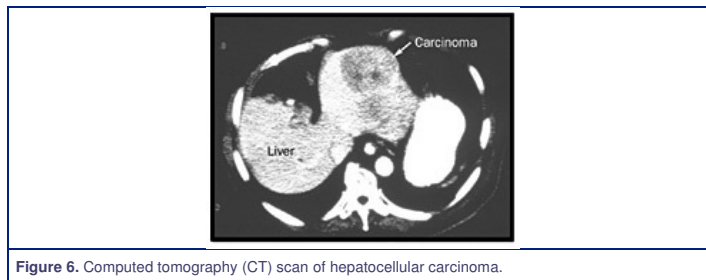
Alpha-Fetoprotein (AFP)

Alpha-fetoprotein levels may be assessed by a blood test. Alpha-fetoprotein (AFP) is a tumor marker that is elevated in 60–70% of patients with hepatocellular carcinoma. Normally, levels of AFP are below 10 ng/ml, but marginal elevations (10–100) are common in patients with chronic hepatitis. However, all patients with elevated AFP should be screened (abdominal ultrasound, CT scan or MRI) for hepatocellular carcinoma, especially if there has been an increase from baseline levels. In our experience, a steadily rising AFP is almost diagnostic of hepatocellular carcinoma. The specificity of AFP is very high when the levels are above 400 ng/ml. Undifferentiated teratocarcinoma and embryonal cell carcinoma of the testis or ovary may give false-positive results and should be considered in the differential diagnosis of elevated AFP.

The doubling time of AFP is around 60–90 days. Therefore, it may be advisable to check AFP every 3–4 months to screen high-risk cirrhotic patients (hepatitis C, hepatitis B, and hemochromatosis) for hepatocellular carcinoma.

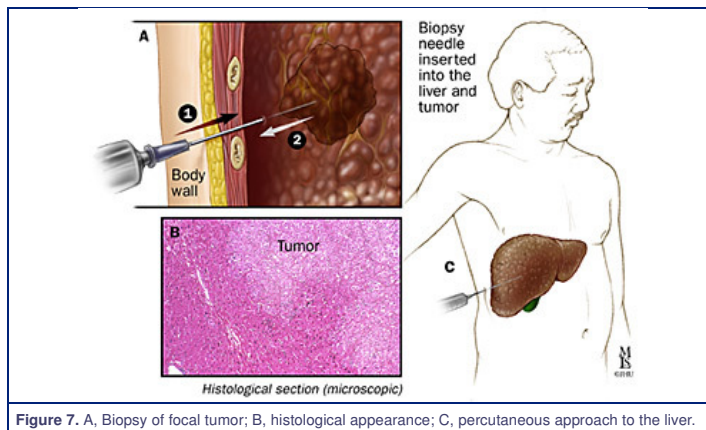
Radiographic Diagnosis

The diagnostic accuracy of ultrasound, CT, magnetic resonance imaging (MRI) and angiography is dependent on a number of variables: expertise of the operator (especially with ultrasound), sophistication of equipment and technique, presence of cirrhosis and, most importantly, experience of the interpreter. For small tumors (<2 cm), the diagnostic accuracy ranges from 60–80%. The diagnostic accuracy increases significantly with an increase in tumor size, ultimately reaching 100% with very large tumors with all modalities (Figure 6).



Liver Biopsy and Histological Grading

Liver biopsy is indicated when diagnosis is in doubt (Figure 7). If AFP is significantly elevated and a tumor is seen in the liver, it is reasonable to assume a diagnosis of hepatocellular carcinoma and a liver biopsy is not warranted.



The World Health Organization has suggested that hepatocellular carcinoma might be classified into histological types based on the structural organization of tumor cells: trabecular or sinusoidal type, pseudoglandular or acinar type, and compact or scirrhous sclerosing agent type. The tumor could also be graded based on the degree of cell differentiation into well, moderately, and poorly differentiated.

| | |
|-----------|---|
| Tx | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Solitary, < 2 cm without vascular invasion |
| T2 | Solitary, <2 cm, with vascular invasion; multiple, one lobe, < 2 cm, without vascular invasion |
| T3 | Solitary, > 2 cm, with vascular invasion; multiple, one lobe, < 2 cm, with vascular invasion; multiple, one lobe, > 2 cm, with or without vascular invasion |
| T4 | Multiple, > one lobe; invasion of major branch of portal or hepatic veins |
| Nx | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis |
| M0 | Distant metastasis is absent |
| M1 | Distant metastasis is present |

Table 1. TNM Staging

Another well-known staging method is UICC (International Union Against Cancer) classification, which is based on tumor number, size, vascular invasion, and metastasis.

Because most liver cancers are observed in association with cirrhosis, it is important to consider the severity of liver disease before a treatment strategy is planned. Child-Pugh scoring determines the severity of liver disease on the basis of serum albumin, bilirubin, prothrombin time, ascites, and encephalopathy.

| Points | 1 | 2 | 3 |
|---|--------|------------------------------------|--|
| Encephalopathy | None | 1-2 | 3-4 |
| Ascites | Absent | Slight, or controlled by diuretics | At least moderate despite diuretic treatment |
| Bilirubin (mg/dL) | <2 | 2-3 | >3 |
| Albumin (g/dL) | ≥3.5 | 2.8-3.5 | <2.8 |
| Prothrombin time (seconds prolonged) | <4 | 4-6 | >6 |
| International normalization ratio | <1.7 | 1.7-2.3 | >2.3 |
| For primary biliary cirrhosis, primary sclerosing cholangitis, or other cholestatic liver diseases: Bilirubin (mg/dL) | <4 | 4-10 | >10 |
| Child | A 5-6 | B 7-9 | C >10 |

Table 2. Child-Turcotte-Pugh(CTP)scoring system to assess the severity of the liver disease

Hepatocellular Carcinoma (Liver Cancer): Therapy

Overview

The optimal management of hepatocellular carcinoma depends on a variety of factors including the size, number, and distribution (unilobar vs. bilobar) of tumors, the relationship of the tumor to hepatic vasculature, the status of distant metastases, the severity of liver disease (Child-Pugh score), the suitability of the patient for liver transplantation, the functional status of the patient, and local expertise. The mean survival of symptomatic patients with hepatocellular carcinoma is approximately 2–3 months. The doubling time of the tumor size is 2–3 months. Optimal management should attempt to prolong without compromising quality of life.

Hepatocellular carcinoma is relatively insensitive to systemic chemotherapy or radiotherapy and, therefore, these options will not be discussed. The following treatment options are available to patients with hepatocellular carcinoma in our center:

- Surgical resection
- Liver transplantation
- Cryosurgery
- Hepatic artery chemoembolization
- Percutaneous ethanol
- Radiofrequency ablation (surgical and percutaneous)
- Cisplatin gel injection

Management should be a team approach.

Surgical Therapy

Surgery is the treatment of choice in noncirrhotic patients with hepatocellular carcinoma—and in cirrhotic patients with well-preserved synthetic functions (Child A). However, only 20% of patients are potentially resectable at the time of presentation. In noncirrhotic patients, surgical mortality is less than 3% in experienced hands, but increases to 8% in patients with cirrhosis. The overall 5-year survival rate after surgical resection is approximately 35% (45% for small tumors, 2–5 cm).

Liver Resection

Surgery provides the best possibility for a cure. For that reason, every patient should be evaluated first and foremost for the possibility of resection. Removing the part of the liver containing the tumor can result in cure and long-term survival in situations in which the cancer is detected early and has not spread within the liver or to other organs (Figure 9).

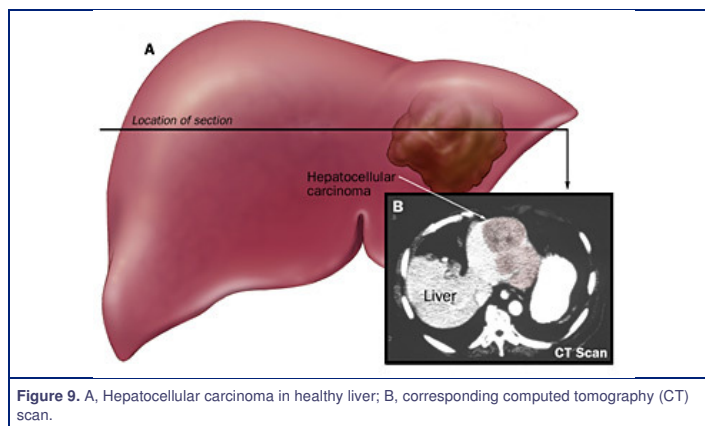


Figure 9. A, Hepatocellular carcinoma in healthy liver; B, corresponding computed tomography (CT) scan.

Unfortunately, not all patients are eligible for liver resection. Resection is not indicated when: 1) the tumor has spread to other parts of the liver or the body, 2) the size or location of the tumor (near major blood vessels) precludes it from being safely removed without compromising function of the remainder of the liver, 3) the associated cirrhosis or disease limits the ability to safely operate upon or remove part of the liver, and 4) other medical conditions make surgery unsafe.

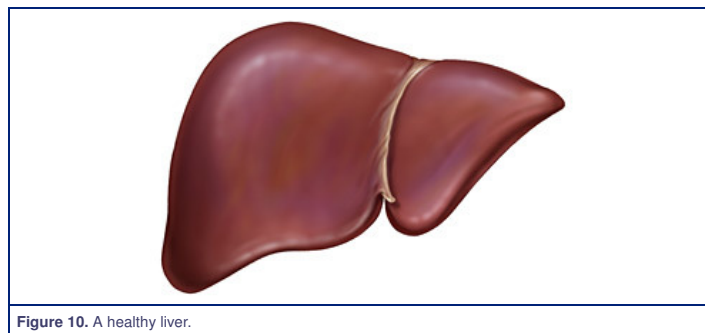


Figure 10. A healthy liver.

The liver has the capacity to regenerate if part of it is removed. In a healthy liver (Figure 10), up to 75% of the liver may be removed and the remaining portion will return to normal size within six months. In livers diseased with cirrhosis (Figure 11), however, the capacity to regenerate is limited, often making extended liver resections more hazardous.

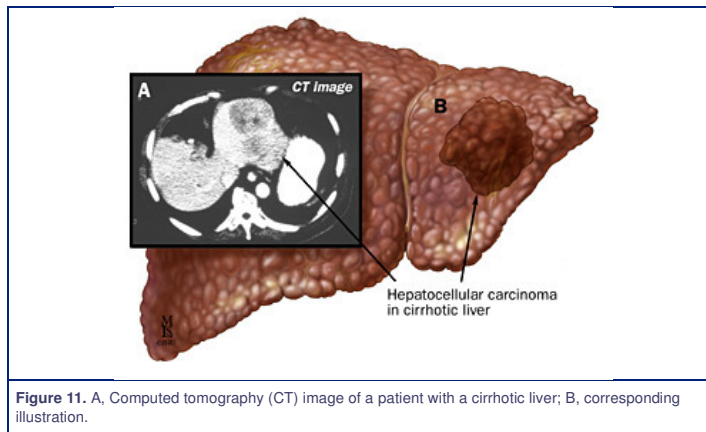


Figure 11. A, Computed tomography (CT) image of a patient with a cirrhotic liver; B, corresponding illustration.

A variety of liver resections can be performed. These include resection of an entire lobe (right or left), more than one lobe (extended lobectomy), or segmental resection (part of a lobe). These resections are based on the eight anatomical segments of the liver (Figure 12).

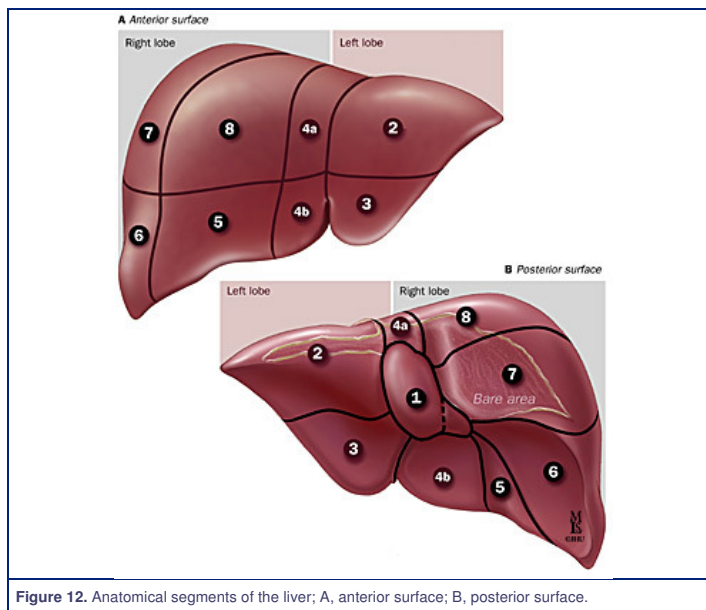


Figure 12. Anatomical segments of the liver; A, anterior surface; B, posterior surface.

Liver resections are surgical procedures carried out under general anesthesia and may take anywhere from 2–5 hours to complete. The incision is usually made on the right side, below the edge of the rib cage. Most patients do not require blood transfusions. Patients are typically hospitalized for 4–6 days.

Resection contraindications include evidence of clinical jaundice in the absence of biliary obstruction, ascites, renal insufficiency, or prolonged prothrombin or partial thromboplastin thrombosis times. The operative mortality is less than 3% for noncirrhotic patients compared with 5–25% for cirrhotic patients, and noncirrhotic patients are resectable in up to 60% of cases. Although most patients with cirrhosis are unresectable, those with Child's A or mild cirrhosis have significantly better outcomes after liver resection than patients with more severe Child's B or C cirrhosis. Although the resectability rate is low and operative mortality higher compared to liver resection for metastatic liver cancer, the 5-year survival rate after resection for hepatocellular carcinoma ranges from 25–65%. Favorable prognostic factors include 1) well-differentiated or fibrolamellar history, 2) absence of vascular invasion, 3) tumors less than 5 cm in diameter.

Operative morbidity and mortality from liver resection has significantly improved in recent decades, principally because of a clearer understanding of anatomic considerations, newer surgical techniques, and improved postoperative care. A variety of types of surgical resections can be performed depending on the extent and location of disease.

Minor hepatic resections include both nonanatomic wedge resections of peripheral lesions and anatomic resection of hepatic segments. Major resections include hepatic lobectomy and extended lobectomy. When performing major hepatic resection, the vascular structures supplying the liver being removed are typically isolated extrahepatically prior to parenchymal dissection. Inflow occlusion at the porta hepatis can be useful in reducing bleeding during parenchymal dissection. The noncirrhotic liver can tolerate occlusion times beyond 60 minutes without irreversible damage. However, such warm ischemia is not tolerated as well in cirrhotic livers. In such cases, total inflow occlusion should be only be used intermittently and for brief periods of time. Total vascular isolation can also be used, incorporating both inflow occlusion and control of the intrahepatic and suprahepatic vena cava. This technique, however, is associated with significant hemodynamic instability and should be used only selectively in complex cases.

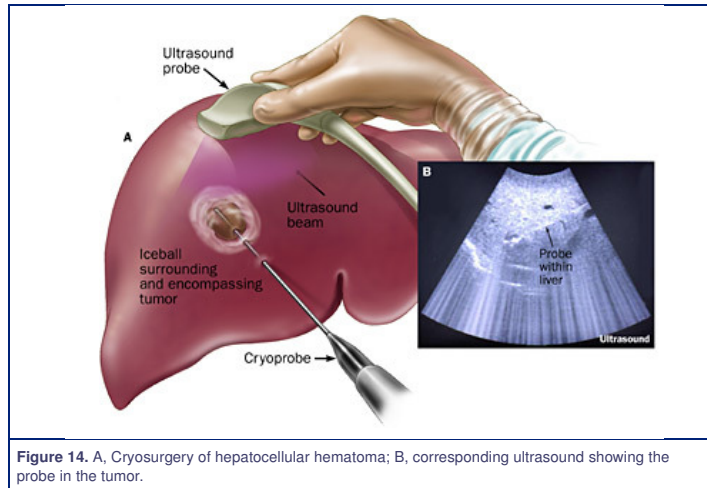
Excessive blood loss during liver resection not only increases the need for blood transfusion, with its associated problems, but increases the risk of structural injury and suboptimal tumor margin clearance by obscuring the surgical field. Newer surgical techniques of vascular isolation, as well as the use of intraoperative ultrasonography, have significantly reduced the need for blood transfusions and blood products in modern liver surgery. The current literature reports that fewer than half of patients undergoing major liver resection require blood transfusions. Other techniques can be used to further reduce the need for allogenic blood transfusion.

Cryosurgery

Although surgical resection may afford the only potential for cure for patients with liver tumors, many patients may not be surgical candidates for a variety of reasons. Novel methods for local ablation have been developed with the goal of increasing the number of patients eligible for surgical therapy. Hepatic cryosurgery is one such

interstitial therapy that has gained popularity in recent years. This technique relies on the in situ destruction of a defined area within the liver using liquid nitrogen at subzero temperatures. Although cryosurgery has been used in the past for the treatment of a variety of surface malignancies, recent advances in the ability to deliver liquid nitrogen deep within tissue using a closed-circuit insulated probe system, as well as improvements in intraoperative imaging using intraoperative ultrasound, have provided the capability for safe hepatic cryoablation .

Cryosurgery is a technique utilizing subzero temperatures to destroy tumors. In most cases, the tumor is destroyed but not removed. The technique involves the placement of one or more probes (cryoprobe) into the tumor using ultrasound to guide the placement. Liquid nitrogen, at -190°C , is circulated in a closed system through the end of the probe creating an ice ball at the tip. The ice ball is allowed to encompass the tumor and approximately one-half-inch margin around it (Figure 14). The tumor is frozen and thawed twice, potentially taking up to 30 minutes. Following completion of the procedure, patients are monitored in the Intensive Care Unit overnight and remain in the hospital for 3–5 days. Cryosurgery is an operative procedure requiring general anesthesia. It may be performed alone or in conjunction with a liver resection.



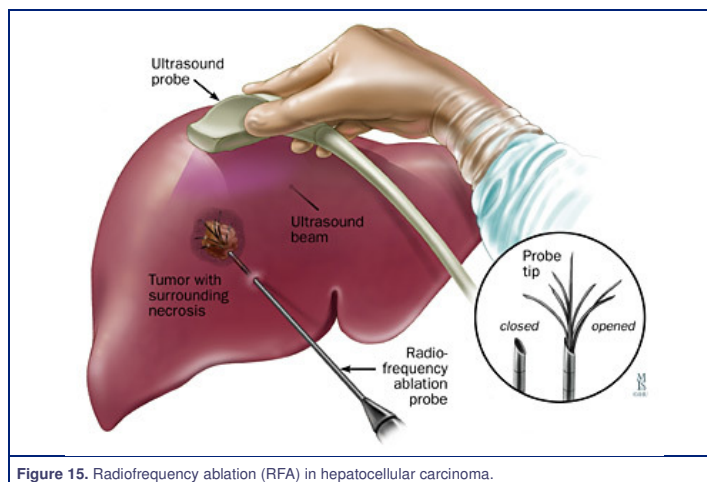
Relative indications for the application of include unresectable patients with multiple tumors, patients with tumors in anatomic locations not amenable to formal resection, patients in whom limited hepatic reserve precludes major liver resection, and patients with associated comorbid disease that may limit their ability to tolerate major liver resection. The upper limit of tumor size that can safely be treated with cryosurgery is approximately 6–8 cm. Often cryosurgery is used in conjunction with liver resection, particularly when low-volume contralateral disease is found at the time of planned resection. Cryosurgery has also been used as adjuvant to liver resection along a close resection, or as a "handle" when performing nonanatomic resections.

Overall, most patients tolerate cryosurgery well. Early reported series suggest that this procedure can be performed safely and with few complications. However, care must be taken to avoid hypothermia and oliguria. Cracking the liver surface during freezing can result in excessive bleeding. Follow-up of early, uncontrolled series of patients suggests that survival results are comparable to those of hepatic resection for both hepatocellular carcinoma and some metastatic tumors. When adequate cryoablation is performed with sufficient (>1 cm) margins, local recurrence in most series is less than 20%.

The major limitation associated with hepatic cryosurgery is the ability to carefully document complete incorporation of the targeted lesion with adequate circumferential margins . In addition, major vascular structures within the liver such as the main portal veins, vena cava, or proximal hepatic veins may provide a "cold sink" which can limit the practitioner's ability to achieve complete freezing in these areas. Tumors located near these structures may not be optimal for cryosurgery. When using this technique for curative intent, precise placement and adequate documentation of complete ablation are important. Caution must also be taken when recommending cryoablation for individuals with a large number of lesions. Although ablation of multiple lesions may be technically possible, the oncological benefit of locally treating multiple lesions is questionable. A more important question may be whether cryosurgery is comparable to resection in patients with resectable disease. Until a well-controlled trial is carried out comparing these two methods, patients with resectable disease should be offered resectional therapy.

Radiofrequency Ablation

Radiofrequency ablation (RFA) is a new technique that makes use of a "heating" probe to destroy tumors within the liver. A thin probe is placed within the tumor, typically under ultrasound guidance. After deploying the tip array, an electrical current is applied, generating heat ($80\text{--}100^{\circ}\text{C}$) that destroys the tumor (Figure 15). RFA is generally indicated for small tumors within the liver and can be applied with minimal side effects. The advantage of this technique is that it can be used either in the operating room with an open or laparoscopic approach, or directly through the skin (percutaneous approach). As with cryotherapy, RFA can be used in conjunction with liver resection. Some of the tumor may be surgically removed, while remaining disease is treated with RFA.



Liver Transplantation

In patients with small tumors and advanced cirrhosis (Child B or Child C) the treatment of choice is liver transplantation (Figure 16).

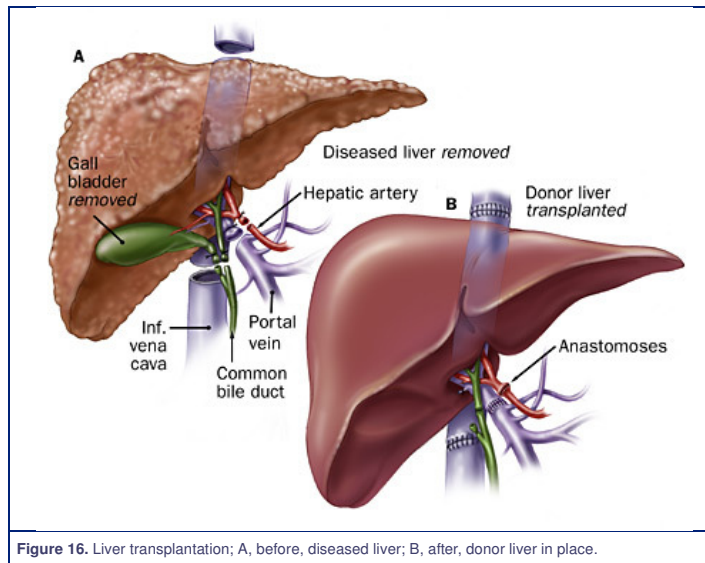


Figure 16. Liver transplantation; A, before, diseased liver; B, after, donor liver in place.

The 5-year survival in patients with small tumors (a single tumor less than 5 cm, or two tumors less than 3 cm) is 50–60%. Poorly differentiated tumors that show vascular invasion, and large tumors have a poor prognosis. Although the presence of tumors of both lobes was at one time considered a poor prognosis after liver transplantation, a recent study demonstrated that patients with bilobar disease have the same survival rates as patients with unilobar disease.

Patients who are not candidates for surgical resection or transplantation should be considered for other forms of treatment including cryosurgery, chemoembolization, ethanol or cisplatin infusion, or radiofrequency ablation (RFA).

For more information: Johns Hopkins Liver Transplantation Web Site

Interventional Radiological Therapy

Hepatic Artery Chemoembolization

Hepatic artery chemoembolization is by far the most commonly performed procedure in the treatment of unresectable liver tumors (i.e., those that are inoperable). Most hepatic tumors are supplied by the hepatic arterial system, as opposed to normal liver tissue, in which most of the blood supply comes from the portal venous system. Chemoembolization has several theoretical advantages over intravenous pump infusion therapy because it delivers highly concentrated drugs to the tumor itself and arrests blood flow, the latter prolonging contact time within the tumor. This technique deprives the tumor of its oxygen supply while achieving a drug concentration in the tumor 10–25 times greater than that which can be achieved by infusion alone. In addition, the "dwell time" for the drug is markedly prolonged, with measurable drug levels present as long as a month after chemoembolization (Figure 17). Up to 85% of the administered drug is trapped in the liver, minimizing systemic toxicity. Extensive data have demonstrated improved patient survival when treated with chemoembolization.

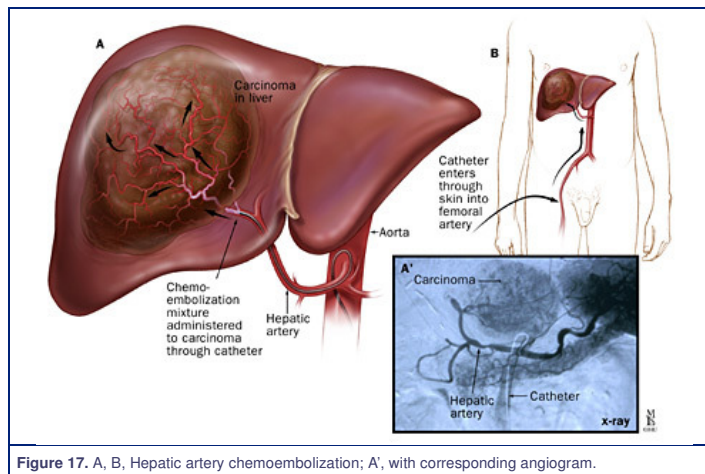


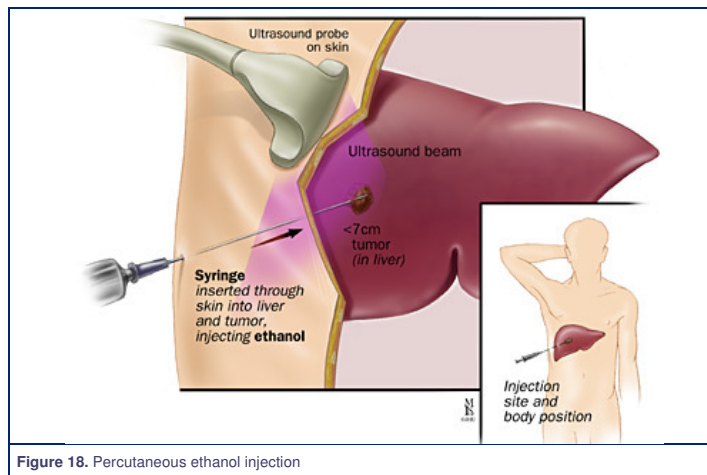
Figure 17. A, B, Hepatic artery chemoembolization; A', with corresponding angiogram.

More recently, chemoembolization has also been applied to patients with metastatic disease confined to the liver. Patients suffering from colon carcinoma frequently develop metastases, with sole involvement of the liver in 10% of the cases. In these cases, arterial chemoembolization is often beneficial. Neuroendocrinetumors have also been shown to benefit from arterial chemoembolization due to the high degree of vascularity. Patients with carcinoid tumors of the liver and carcinoid syndrome experience improvement in tumor characteristics and tumor markers, as well as a significant reduction in the carcinoid symptoms after undergoing arterial chemoembolization.

Chemoembolization has become the treatment of choice for unresectable hepatocellular carcinoma as well as neuroendocrine tumors of the liver, and the procedure shows promise against colorectal metastases.

Percutaneous Ethanol Injection

Ultrasound-guided percutaneous ethanol injection in hepatic tumors was first described in 1983. Percutaneous ethanol injection has been used primarily to treat tumors less than 5 cm in diameter and patients with less than three lesions. It has been demonstrated that ethanol injection is more effective against hepatoma lesions than against metastatic lesions (Figure 18).

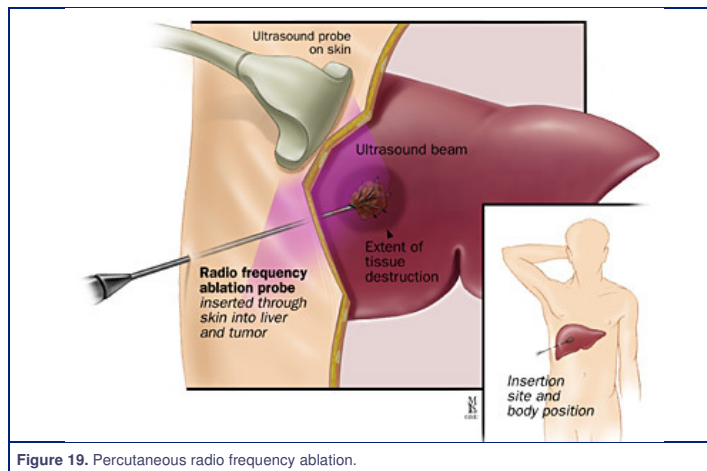


The procedure is performed under ultrasound guidance. A small needle is inserted into the posterior aspect of the tumor, and ethanol is slowly injected into the lesion. Patients may receive one or two sessions per week until the tumor is completely saturated. Post-procedural imaging, including CT and MRI, is typically conducted after 1 month—and then every 4? months thereafter.

Recently published data have shown significant increases in the survival rate of patients diagnosed with hepatocellular carcinoma confined to one single small lesion, without underlying liver disease. The results are less impressive for patient with larger tumors, and those suffering from metastatic colon cancer.

Percutaneous Radio Frequency Ablation

Percutaneous radio frequency ablation causes local tissue destruction by frictional heat. When the temperature surpasses 90 °C, an immediate destructive effect occurs within the tumor. This technique was first described in 1993 and is one of the most recent additions to the armamentarium against liver tumors (Figure 19).



This procedure is also performed under ultrasound guidance. A radiofrequency needle is inserted deep into the lesion and multiple electrodes are deployed. The generator is then activated to achieve high temperatures within the tumor. The duration of the treatment varies from 6–15 minutes.

Only limited data are available regarding use of this technique to treat unresectable liver tumors, but preliminary studies have shown a trend toward prolonged survival.

Cisplatin Gel Infusion

Percutaneous cisplatin gel infusion is a new and promising therapeutic option for the treatment of unresectable liver tumors (Figure 20).

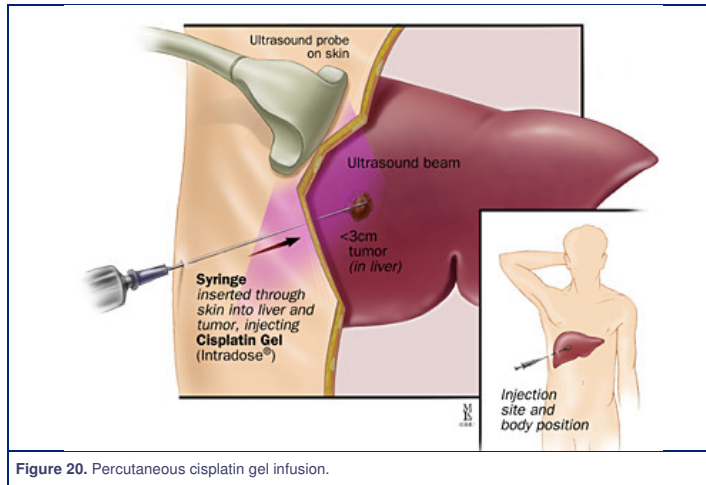


Figure 20. Percutaneous cisplatin gel infusion.

This technique was recently developed and is currently undergoing clinical trials in the United States. It is similar to percutaneous ethanol injection in that it is performed under ultrasound guidance. A small needle is inserted directly into the deepest aspect of the tumor and the cisplatin gel is infused. The gel slowly diffuses throughout the tumor and acts as a carrier of the chemotherapeutic drug. Because this treatment method is undergoing initial clinical trials, strict enrollment criteria have been defined. Tumors greater than 7 cm cannot be treated using this technique. Early data from Europe and Asia are promising, but further evaluation is needed.

Prevention

Most patients with hepatocellular carcinoma present very late for any effective treatment. Screening for hepatocellular carcinoma may improve outcomes by detecting small tumors. To make a major impact on the mortality of hepatocellular carcinoma worldwide, a cheap, yet sensitive diagnostic tool, and an equally effective treatment, must be made available. Approximately 300–400 million people are carriers for hepatitis B virus. Effective screening should be directed toward high-risk patients as well as those with hepatitis C and hemochromatosis. AFP and ultrasound are neither cheap nor sensitive diagnostic methods for large populations. Another strategy may be to screen only those patients with viral hepatitis and cirrhosis. However, in areas where hepatocellular carcinoma is common, silent cirrhosis is present in over 50% of patients who present with hepatocellular carcinoma. Therefore, any screening modality aimed at patients with cirrhosis will exclude more than 50% of high risk-patients. Moreover, even in the best hands, surgical resection only provides a 5-year survival rate of 40%. The surgical expertise necessary to obtain these results is not available in many countries with high incidence rates. Therefore, we are unlikely to see any major impact on hepatocellular carcinoma in the world through early detection. It is more likely that we may see a major decline in the incidence of disease by universal vaccination for hepatitis B virus (and perhaps in the future for hepatitis C virus) or better eradication of hepatitis B and C viruses with medical treatment and removal of aflatoxins from food products.

Future

Despite many advances, the treatment of hepatocellular carcinoma is unsatisfactory. In the future, gene therapy and immunotherapy may become available for the management of hepatocellular carcinoma. Until then, every effort should be directed toward prevention (hepatitis B virus vaccination) and early diagnosis (screening of high-risk subjects).