# Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC), is one of the world's most common and deadly cancers, and is the most frequently observed solid tumour of the liver (França et al., 2004). Its aggressive nature and ability to metastasize leads to a poor patient prognosis. HCC accounts for nearly one million annual deaths globally, and has shown an increased incidence in North America over the past decade. The five-year survival rate for untreated patients is less than five percent (Bosch et al., 1999). A brief exploration of the etiology, structural and functional alterations of the liver, and treatment options currently in trial will permit an improved understanding of this ubiquitous illness.

## Etiology

Cirrhosis is considered the most central risk factor in predicting this cancer. Found in approximately 80% of all cases, cirrhosis involves the replacement of hepatocytes (functional cells of the liver cells) with fibrous tissue and disruption of normal blood flow throughout the liver (Ulmer, 2000). Identification and subsequent follow up of cirrhosis is often required to diagnose the presence of a tumour. Alcohol consumption is a well-known causative factor of cirrhosis. Although a direct carcinogenic link between alcohol and the liver has yet to be elucidated, there is increasing evidence to support the correlation (França et al., 2004). Males, who are heavier consumers of alcohol than women, are eight times more likely to develop HCC than females in regions of the world where there is a high prevalence of the cancer (MD Consult, 2004). In addition to alcohol, certain plants, synthetic pharmaceutical agents, and industrial pollutants have demonstrated causative capacities for HCC in animal models and human studies. Aflatoxin B and vinyl chloride have received attention as two of the most prevalent industrial carcinogens (Akriviadis et al., 1998).

In African and South Asian nations, hepatitis B is the primary cause of HCC (França et al., 2004). Regardless of the presence of cirrhosis, HCC develops among young patients because hepatitis B virus infection usually occurs early in life. The prolonged time frame provided for the infection to disseminate eventually provides an environment conducive to the establishment of liver tumours. In the Western World, infection with the hepatitis C virus acts as a major causative agent for HCC development (Gross, 1998).

## A Brief Interlude

Cancer results when genes that control the cell cycle mutate. This alteration in DNA may cause the entire cell to lose control of its reproduction cycle, and a substantial increase in the ability to grow and reproduce ensues (Arcturus, 2004). A cell with one mutation has a greater probability of undergoing a further mutation, and so a cycle is initiated which culminates in a complete loss of mitotic control (Arcturus, 2004).

Angiogenesis is a characteristic of many tumours, permitting a sustained supply of nutrients and oxygen (Fuchs & Pritchard, 2002). Angiogenic growth factors are similar to those present in embryonic development, wound healing, and normal tissue growth (Vascular Endothelial Growth Factor, 2000). This process of blood vessel development and proliferation aids in the metastasizing of the primary tumour. In HCC, the main sites of metastases include the lungs, bones, and adrenal glands (França et al., 2004).

## Changes To The Organ And Organism

Patients with HCC typically display symptoms of right upper quadrant pain, weight loss, and general weakness (França et al., 2004). However, HCC is often tested for in any patient with chronic liver disease, permitting the early initiation of treatment if a tumour is located. Other patients are not diagnosed until the tumour is well advanced and exceeds a diameter of 10 cm (Ulmer, 2000). Acute abdominal pain and intra-abdominal bleeding resulting from rupture of the liver tumour are scenarios which also favor the diagnosis of HCC (Befeler & Di Biscelgie, 2002).

The liver consists of two large lobes. Each lobe is composed of many lobules, considered the functional units of the liver (Tortora & Grabowski, 2003). Each lobule consists of numerous hepatocytes which branch in an

irregular and interconnected fashion around a large central vein. The liver receives blood from two sources. The first, the hepatic artery, presents the liver with oxygenated blood, while the second, the hepatic portal vein, brings nutrient-rich deoxygenated blood. This blood drains into the liver sinusoids, then the central vein, hepatic vein, and finally into the right atrium of the heart via the inferior vena cava. Among the many functions of the liver, the production of bile is fundamental. This yellow-green liquid is required for lipid emulsification and absorption in the small intestine (Tortora & Grabowski, 2003).

HCC affects the structural appearance and functional capabilities of the liver. The growing tumour takes on a histology characterized by alterations to trabecular structures. The trabeculae become encased in an endothelial lining and are separated from other trabeculae by sinusoid-like channels (Mitros, 2004). Bile, carbohydrate, lipid, and protein metabolism are all affected by the presence of a tumour. The ability to adequately process and detoxify drugs may be jeopardized, depending on the size and location of the tumour (Tortora & Grabowski, 2003). A deficiency in the coagulation factors produced in the liver suggests a generally limited synthetic capacity of the organ, and may limit the ability of the blood to clot following injury (Hepatocellular Carcinoma Diagnosis and Management, 2004). Patients with HCC typically have elevated levels of alkaline phosphatase, indicative of biliary obstruction (Hepatocellular Carcinoma Diagnosis and Management, 2004). Massive lesions or enlargements in the liver, as well as the circulation of free fluid around the organ, are further HCC characteristics that impact normal functioning.

## Staging And Diagnosis

The diagnosis, staging, and treatment of HCC are three factors which are intimately linked. Treatment is effective only if it is received at a specific developmental stage.

Ultrasound is the superior technique for diagnosing focal hepatic lesions; it allows physicians to identify tumours in early stages (Ebara et al., 1989). Nodule size is the primary HCC characteristic which accounts for differential ultrasonographic images. Ultrasound sensitivity is approximately 40% for tumours less than one centimeter in diameter. Tumours of greater size have values which exceed 95% (Bizollon et al., 1998). These sensitivity values increase when ultrasound is used in conjunction with Doppler, which measures the flow rate of blood. This combination permits the identification of tumour thrombosis and the presence of hepatofugal pulsatile flow and intratumoural necrosis (Tanaka et al., 1993).

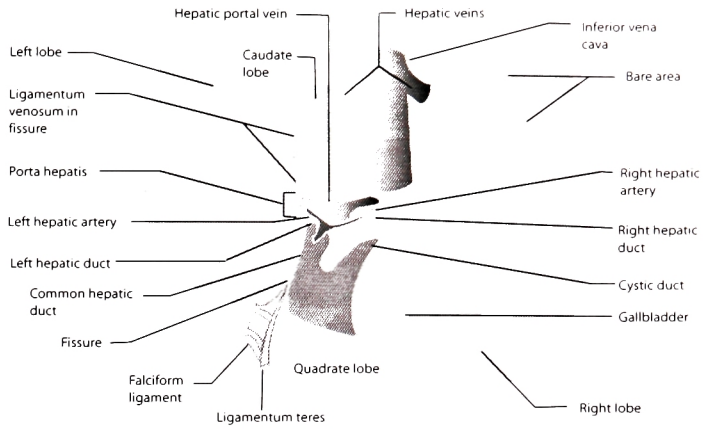


**Figure 1:** Anatomical illustration of the posterior aspect of the liver.

Helicoidal computed tomography (HCT) is a sensitive diagnostic tool often used following the detection of HCC by ultrasound (França et al., 2004). Combining HCT images with intravenous contrast provides a greater level of sensitivity when identifying individuals with HCC. The accuracy of computed tomography permits the identification of metastasized tumour in both lymph nodes and the vascular system, providing a more holistic picture of the illness (França et al., 2004).

Histopathological measurements are presently the most accurate means of diagnosing HCC (Ebara et al., 1989). Fine needle aspirative biopsy is a common procedure used to collect liver samples for histolopathology. This technique alone has demonstrated specificity between 90 and 100%, and through combinations with the aforementioned diagnostic tools, the accuracy of HCC diagnosis will be undoubtedly enhanced (Ebara et al., 1989).

The staging of HCC is a complex procedure. Numerous classification systems are in place to stage the disease and to subsequently determine the prognosis. These classification systems, including those of the Barcelona Clinic Liver Cancer (BCLC) Group (Llovet et al., 1999) and the Cancer of the Liver Italian Program, consider the degree of hepatocellular dysfunction, often considered the primary prognostic variable (França et al., 2004).

## Treatment And Prevention

Many cancer treatments are invasive and lengthy, and thus significantly impact the quality of life of patients. Chemoembolization and complete liver transplantation are two common treatment options for patients with HCC.

Chemoembolization relies on the knowledge that most HCC tumours receive nutrients from the liver's arterial system (França et al., 2004). Thus, blocking the hepatic artery is a definitive mode of treatment which has demonstrated great promise. As a non-surgical technique, chemoembolization utilizes interventional radiology to occlude the hepatic artery following identification with fluoroscopy (Befeler & Di Biscelgie, 2002). This technique effectively causes ischemic necrosis of approximately 80% of tumours, while leaving viable the unaffected hepatocytes and cells of the portal vein (França et al., 2004). Because of the specificity of this procedure, there is a realistic potential that high doses of chemotherapeutic agents may be delivered to the tumour with the result of high extraction rates following only one round of administration (Befeler & Di Biscelgie, 2002). The only clear limitation of this approach is that the blocking and chemotherapeutic agents must be re-administered every few months to maintain adequate functional levels in the liver.

When the affected liver has lost function and can no longer be treated by surgical resection, total liver transplantation is the recommended treatment for patients with HCC (Befeler & Di Biscelgie, 2002). Cases in which there is a small, single tumour, free of distant metastases and vascular invasion often have very encouraging prognoses following liver transplantation. Since the entire liver is replaced, any primary liver diseases are effectively removed along with the neoplasia. The limitation of this method lies in the extremely low number of liver donors (Bruix & Llovet, 2002). This creates a cascade effect which increases both the time on waiting lists and the monetary cost of the procedure to patients (França et al., 2004).

### Conclusion

Preventing or modifying the risk factors associated with HCC is a critically important, yet often overlooked, means of decreasing the incidence of this cancer. The dissemination of information concerning lifestyle choices enables individuals to make healthier decisions in their daily lives (MD Consult, 2004). Tobacco and alcohol use have demonstrated a correlation with the presence of cirrhosis, and cirrhosis itself is the primary risk factor for the development of HCC (MD Consult, 2004). Drug abuse, an activity which substantially increases the risk of hepatitis B and C exposure, is a further lifestyle choice which can influence the presence of HCC. Furthermore, environmental carcinogenic agents should be avoided, participation in vaccination programs for hepatitis should be practiced, and screening programs should be attended by individuals who are aware of a family history of liver disease (MD Consult, 2004).

# Congenital Insensitivity to Pain with Anhidrosis (CIPA)

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It is very easy to recognize. It is known all over the world and it breaks all language barriers. It is referred to as pain. This unpleasant experience notifies an individual that something is wrong in the body and needs to be corrected. It also serves a protective function by signalling the presence of harmful agents that may damage the body of an individual. However, pain is a complex perception that differs enormously amongst individuals (Tortora and Grabowski, 2003).

### Pain, Nociception And CIPA

The perception of pain, referred to as nociception, depends on receptors and pathways that are specific to this sensation. Pain sensation begins in response to the stimulation of relatively unspecialized nerve cell endings called nociceptors (Tortora and Grabowski, 2003). Once nociceptors are stimulated, they convert a variety of stimuli into action potentials. They are then carried by nerve fibres to the spinal cord and the brain, where the nerve impulse is interpreted as pain (Tortora and Grabowski, 2003 & Purves et al., 2001).