

Primary Hepatocellular carcinoma: management and prognosis

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Abstract: Hepatocellular carcinoma (HCC) causes high mortality worldwide with 50 per cent of them in China. HCC cases are as a result of a viral hepatitis (hepatitis B or hepatitis C), metabolic toxins such as alcohol or aflatoxin, conditions like hemochromatosis and alpha 1-antitrypsin deficiency or non-alcoholic steatohepatitis (NASH). The high prevalence rate of hepatitis C virus (HCV) occurs in African and Asian countries. The markers of hepatitis C infection (positive-anti HCV) are found in 80% - 90% patients in Japan, 70% in Egypt, 40- 50% in Pakistan and 35-40% in Saudi Arabia. China is classified as high endemic area with 8% - 20 % prevalence of hepatitis B virus (HBV). Other Asian countries are characterized as moderate to high prevalence rate of HBV in their population. The prevalence of HBV infection in children has declined in countries since the beginning of the vaccination. Chronic infections of hepatitis B and/or C can aid the development of HCC by repeatedly causing body's immune system to attack the liver cells, some of which are infected by the virus. Aflatoxin is a carcinogen and aids carcinogenesis of HCC in the liver. Ultrasound and imaging modalities are used to aid in the diagnosis. Therapies include surgical resection, interventional radiology, and liver transplant. Prognosis for metastatic or unresectable HCC has improved due to sorafenib (Nexavar®). Prevention of hepatitis B or C infection, childhood vaccination, reduce alcohol intake and avoiding the risk factors is the key to prevent HCC.

Keywords: Hepatocellular carcinoma, Hepatitis B virus, Management, Prognosis

I. Introduction

Hepatocellular carcinoma (HCC), also called malignant hepatoma is the most common type of liver cancer [1]. HCC causes 662,000 deaths worldwide per year, about half of them in China. [2]. Most cases of HCC are as a result of either a viral hepatitis (hepatitis B or C), metabolic toxins such as alcohol or aflatoxin, conditions like hemochromatosis and alpha 1-antitrypsin deficiency or non-alcoholic steatohepatitis (NASH) [1]. HCC is relatively uncommon in the United States and many developed countries. It occurs most commonly in countries where hepatitis B are common [3]. HCC may directly present with yellow skin, bloating from fluid in the abdomen, easy bruising from blood clotting abnormalities, loss of appetite, unintentional weight loss, abdominal pain especially in the right upper quadrant, nausea and vomiting or feeling tired [4]. Many imaging modalities are used to aid in the diagnosis of hepatocellular carcinoma [5]. Frequently used therapies include, surgical resection [6], interventional radiology (IR), [7], radiofrequency ablation (RFA) [8], a receptor tyrosine kinase inhibitors [9], and liver transplant [10]. Treatment options for HCC and prognosis are dependent on many factors but especially on tumor size, staging, and extent of liver injury. High grade tumor will have poor prognosis [3]. Prevention by reducing exposure to risk factor for liver cancer and vaccination against hepatitis B virus. The paper reviews the prevalence, diagnosis, and management of Hepatocellular carcinoma. -

II. Prevalence

HCC is the most common tumors worldwide. The prevalence of HCC exhibits two main patterns, one in North America and Western Europe and other non-Western countries in Sub-Saharan Africa, central and Southeast Asia, and the Amazon basin. Males are affected more than females usually and it is most common between age of 30 to 50 [11]. In sub-Saharan Africa and Southeast Asia, HCC is the most common cancer, generally affecting more men than women, and the age of onset between late teens and 30s. This variability is in part due to the different patterns of hepatitis B and hepatitis C transmission in different populations - infection at or around birth predispose to earlier cancers than if people are infected later. The time between hepatitis B infection and development into HCC can be years, even decades, but from diagnosis of HCC to death the average survival period is 5.9 months according to one Chinese study during the 1970-80s, or 3 months (median survival time) in Sub-Saharan Africa according to Manson's text book of tropical diseases. HCC is one of the deadliest cancers in China where chronic hepatitis B is found in 90% of cases. In Japan, chronic hepatitis C is

associated with 90% of HCC cases. Food infected (contaminated) with *Aspergillus flavus* (especially peanuts and corns stored during wet seasons) which produces aflatoxin poses risk factor for HCC[2,11].

Asia previously has been classified as high endemic area; China is now the only country. Classified as high endemic area with 8% - 20% prevalence of hepatitis B virus(HBV)[12].Oman, Yemen and Jordan in the Middle East are characterized by a moderate to high prevalence rate of HBV in their own populations[12].Countries with intermediate endemicity in Asia includes; India, Taiwan, Thailand, Philippines,Korea,Iraq,and United Saran Emirates, and countries with low endemicity including Japan, Pakistan, Singapore, Sri Lanka, Bangladesh, Malaysia, Iran, Kuwait and Bahrain[13].Saudi Arabia and Malaysia, the prevalence of HBV infection in children have declined since the beginning of the vaccination [14].Iran is located in low risk area and characterized as low incidence rate of HCC(< 5 per 100,000)[15].

In Asia 170 to 200 million people are infected with Hepatitis C virus (HCV) worldwide and it plays an important role in HCC especially in regions where HCV is less common [16].In developing countries blood transfusion is the main risk for HCVtransmission. Sexual and maternal-infant HCV transmission can occur but it is rare [17].Generally the population at risk for HCV infections who are exposed to infected blood,hemodialysis,IDU,prisoners, tattooing, and during medical and dental care[18].The high prevalence rate of HCV occurs in African and Asian countries(5.3% in Africa and 2.15- 3.9% in Asia)[19].The prevalence of HCV infection in Asian countries varies geographically. InJapan,SaudiArabia, Egypt and Pakistan,HCV is the cause of HCC.The markers of hepatitis C infection(positive anti-HCV) are found in 80%-90% patients in Japan,70% in Egypt,40-50% in Pakistan and 35%-40% in Saudi Arabia[20,21].

Most malignant tumors of the liver discovered in Western patients are metastasis (spread) from tumors elsewhere [11].In the West, HCC is generally seen as a rare cancer, normally of those with pre-existing liver disease. It is often detected by ultrasound screening and so can be discovered by health-care facilities much earlier than in developing regions such as Sub-Sharan Africa[11].Acute and chronic porphyrias (acute intermittent porphyria, porphyria cutaneatarda,hereditarycoproporphryia,variegate porphyria)and tyrosinemia type 1 are risk factors for hepatocellular carcinoma. The diagnosis of acute hepatic porphyria (AIP,HCP,VP) should be sought in patients with hepatocellular carcinoma without typical risk factors of hepatitis B or C,alcoholic liver cirrhosis or hemochromatosis. Both active and latent genetic carriers have developed the cancer at a later age than those with classic symptoms. Patients with acute hepatic porphyrias should be monitored for hepatocellular carcinoma [11].

III. Predisposing factors

The most important predisposing or risk factors vary widely from country to country. In countries where Hepatitis B is endemic, such as China, Hepatitis B is the predominant cause of Hepatocellular carcinoma[22].Whereas in countries, such as United States, where Hepatitis B is rare because of high vaccination rates, the major cause of HCC is cirrhosis(often due to hepatitis C,obesity or alcohol abuse)[22].The main predisposing-risk factors for HCC includes: alcoholism, HepatitisB,Aflatoxin,Hepatitis C(25% of causes globally),[23],cirrhosis of liver, non-alcoholic steatohepatitis(if progression to cirrhosis has occurred) [24], hemochromatosis,alpha 1-antitrypsin deficiency, Wilson's disease(while some theorize the risk increases[25,wp,6],case studies are rare[26],and suggest the opposite where Wilson's disease actually confer protection)[27],type 2 diabetes(probably aided by obesity[28],and hemophilia[29].

The risk of HCC in type 2 diabetes is greater (from 2.5 to 7.1 times the non-diabetic risk)[28,30],depending on the duration of diabetes and treatment duration. A suspected contributor to this increased risk is circulating insulin concentration such that diabetics with poor insulin control or on treatment that elevate their insulin output(both states that contribute to higher circulating insulin concentration)show far greater risk of HCC than diabetics on treatment that reduce circulating insulin concentration[28,30].On this note, some diabetics who engage in tight insulin control(by keeping it from being elevated) show risks level low enough to be indistinguishable from general population[30,,31].This phenomenon is thus not isolated to diabetes mellitus type 2 since poor insulin regulation is also found in other conditions such as metabolic syndrome(specifically when evidence of non-alcoholic fatty liver disease or NAFLD is present)and again there is evidence of greater risk here too[32].While there are claims that anabolic steroids abusers are at greater risk, theorized to be due to insulin and IGF(Insulin like growth factor)exacerbation[33,34],the only evidence that has been confirmed is that anabolic steroids users are more likely to have hepatocellular adenomas(a begin form of HCC)transform into more dangerous HCC[35].

When hepatocellular adenomas grow to a size of more than 6-8cm,they are considered cancerous and thus become a risk of HCC. Although HCC most commonly affects adults, children who are affected with biliary atresia, infantile cholestasis, glycogen-storage disease, and other cirrhotic diseases of the liver are predisposed to developing HCC. Children and adolescents are unlikely to have chronic liver disease; however, if they suffer from congenital liver disorders, this fact increases the chance of developing HCC [36].

Aflatoxin is mycotoxin produced by *Aspergillus flavus*. This fungus grows easily on foodstuffs including peanuts, pistachio, etc., which stored in warm and damp conditions [37]. Studies have been done in Sub-Saharan Africa and South-East Asia revealed the association between aflatoxin and HCC [38]. Also, some studies in Asia, Shanghai and Taiwan, hepatitis B infection and a study in Taiwan reported that in HBsAg carriers, who were susceptible to aflatoxin, were more likely to develop HCC [39].

Alcohol generally contributed to 15 to 45% of HCC cases in the developed countries due to significant role in cirrhosis [40]. Many studies have shown the association of heavy alcohol intake (>50-70 g/d for several years) and HCC [41].

The risk of HCC in obese patients (with body mass index (BMI) greater than 30) is increasing than cirrhotic patients [42]. The prevalence of obesity in adults in South-East Asian countries is low, compared to developed countries like as the United State, but in contrast to South-East Asian countries, the prevalence of obesity in Middle-East countries is high and almost is equal to developed countries. In the future, obesity may be play as an important role of HCC because of the high prevalence in Middle-East countries [43].

IV. Pathophysiology

HCC like any other cancer develops when there is mutation to the cellular machinery that causes the cell replicate at a higher rate and/or results in the cell avoiding apoptosis. In particular, chronic infections of hepatitis B and/or C can aid the development of HCC by repeatedly causing body's own immune system to attack the liver cells, some of which are infected by the virus, other merely bystanders [44]. While this constant cycle of damage followed by repair can lead to mistakes during repair which in turn lead to carcinogenesis, this hypothesis is more applicable, at present, to hepatitis C. Chronic hepatitis C causes HCC through the stage of cirrhosis. In chronic hepatitis B, however, the integration of the viral genome into infected cells, can directly induce a non-cirrhotic liver to develop HCC [44]. Alternative, repeated consumption of large amounts of ethanol can have a similar effect. The toxin aflatoxin from certain *Aspergillus* species of fungus is carcinogen and aids carcinogenesis of hepatocellular cancer by building up in the liver. The combined high prevalence of rates of aflatoxin and hepatitis B in settings like China and West Africa has led to relatively high rates of hepatocellular carcinoma in these regions. Other viral hepatitis such as hepatitis A have no potential to become a chronic infection and thus are not related to hepatocellular carcinoma [44].

V. Diagnosis

HCC most commonly appears in person with chronic viral hepatitis (hepatitis B or C, 20%) or/and with cirrhosis (80%). These people undergo surveillance with ultrasound (US) due to cost effectiveness. Alpha-fetoprotein (AFP) is a marker that is useful if it is markedly elevated. At levels less >20 sensitivity is 41-65% and specificity is 80-94%. However, at levels >200 sensitivity is 31, and specificity is 99% [45].

Ultrasound and Imaging

Ultrasound (US) is often first imaging and screening modality used. On US, HCC often appears as a small hypo-echoic lesion with poorly defined margins and coarse irregular internal echoes. When the tumor grows, it can sometimes appear heterogeneous with fibrosis, fatty change, and calcifications. This heterogeneity can look similar to cirrhosis and the surrounding parenchyma [46].

In people with higher suspicion of HCC (such as rising alpha-fetoprotein and des-gamma carboxyprothrombin levels) [47], the best method of diagnosis involves a CT scan of the abdomen using intravenous contrast agent and three-phase scanning (before contrast administration, immediately after contrast administration, and again after a delay) to increase the ability of the radiologist to detect small or subtle tumors. It is important to optimize the parameters of the CT examination, because the underlying liver disease that most people with HCC have can make the findings more difficult to appreciate [47].

An alternative to CT imaging study would be Magnetic Resonance Imaging (MRI). MRI has about the same sensitivity for detecting HCC as helical CT. However, MRI has the advantage of delivering high resolution images of the liver without nephrotoxic or ionizing radiation [46]. Despite the advantages of MRI, helical CT remains the technique of choice among radiologists due to high cost and long image acquisition time of MRI [46].

Classification

Classification of HCC on CT Liver Image Reporting and Data System (LI-RADS) is the new way to standardize/classify the HCC lesion found on CT and MRI. Radiologist use this classification system in their imaging reports in order further characterize suspicious lesions. As a general introduction, LR1 and LR2 get continued surveillance. LR3 has variable follow up. LR 4 gets close follow up, additional imaging or treatment. LR5 gets treatment [48]. On CT, HCC can have three distinct patterns of growth:

- a) A single large tumor
- b) Multiple tumors
- c) Poorly defined tumor with an infiltrative growth pattern.

A biopsy is not needed to confirm the diagnosis of HCC if certain imaging criteria are met[48].

Histopathology

Macroscopically, liver cancer appears as a nodular or infiltrative tumor. The nodular type may be solitary (large mass). Or multiple (when developed as a complication of cirrhosis). Tumor nodules are round to oval, grey or green (if the tumor produces bile), well circumscribed but not encapsulated. The diffuse type is poorly circumscribed and infiltrates the portal veins, or hepatic vein (rarely). Microscopically, there are four architectural and cytological types (patterns) of hepatocellular carcinoma: fibro lamellar, pseudo glandular (adenoid), pleomorphic (giant cell) and clear cell. In well differentiated forms, tumor cells resemble hepatocytes, form trabeculae, cords and nests, and may contain bile pigment in cytoplasm. In poorly differentiated forms, malignant epithelial cells are discohesive, pleomorphic, anaplastic, giant. The tumor has a scant stroma and central necrosis because of poor vascularization[49].

Staging

The prognosis of HCC is affected by the staging of the tumors as well as the liver's function due to the effects of liver cirrhosis [50]. There are a number of staging classifications for HCC available; however, due to the unique nature of the carcinoma in order to fully encompass all the features that affect the categorization of the HCC, a classification should incorporate tumor size and number, presence of vascular invasion and extrahepatic spread, liver function (levels of serum bilirubin and albumin, presence of ascites and portal hypertension) and general health status of the patient (defined by ECOG classification and the presence of symptoms)[50]. Out of all staging classification systems available, the Barcelona Clinic Liver Cancer (BCLC) staging classification encompasses all of the above characteristics. This staging classification can be used in order to select people for treatment [51]. The important features that guide treatment include: size, spread (stage), presence of tumor capsule, presence of hepatic metastases, presence of daughter nodules and vascularity of the tumor. MRI is the best imaging method to detect the presence of a tumor capsule [51].

VI. Management

Liver transplant: Liver transplant to remove the diseased liver with a cadaveric liver or a living donor graft has historically low survival rates (20% - 36%). During 1996- 2001 the rate has improved to 61% likely related to adoption of the Milan criteria at US transplantation centers. Expanded Shanghai criteria in China resulted in overall survival and disease-free rates similar to the Milan criteria [52].

Receptor tyrosine kinase inhibitor: A receptor tyrosine kinase inhibitor, Sorafenib, approved by the USFDA in December 2005 and in Europe in July 2006, may be used in patients with advanced HCC[53]. Sorafenib is a small molecule that inhibits tumor-cell proliferation and tumor angiogenesis. It has been shown in a Spanish phase III clinical trial to add two months to the lifespan of late stage HCC patients with well-preserved liver function[54].

Surgical resection: Surgical resection to remove a tumor together with surrounding liver tissue while preserving enough liver remnants for normal body function. This treatment offers the best prognosis for long-term survival, but only 10-15% of patients are suitable for surgical resection. This is often because of extensive disease or poor liver function. Singapore Liver Cancer Recurrence (SLICER) score can be used to estimate risk of recurrence after surgery [55].

Interventional Radiology (IR) includes: Transcatheter arterial chemoembolization (TACE), Radiofrequency ablation, Selective internal radiation therapy, Intra-arterial iodine-131, Percutaneous ethanol injection (PEI), Combined PEI and TACE, and portal vein Embolization (PVE).

Transcatheter arterial chemobolization (TACE) is usually performed for unresectable tumors or as a temporary treatment while waiting for liver transplant. TACE is done by injecting an antineoplastic drug (e.g., cisplatin) mixed with a radiopaque contrast (e.g., Lipiodol) and an embolic agent (e.g., Gelfoam) into the right or left hepatic artery via the groin artery. TACE has been shown to increase survival and to down stage HCC in patients who exceed the Milan criteria for liver transplant [56].

Radiofrequency ablation (RFA) uses high frequency radio-waves to destroy tumor by local heating. The electrodes are inserted into the liver tumor under ultrasound image guidance using percutaneous, laparoscopic or open surgical approach. It is suitable for small tumors (<5cm). RFA has the best outcomes in patients with a solitary tumor less than 4cm [57].

Selective internal radiation therapy (SIRT) can be used to destroy the tumor from within (thus minimizing exposure to healthy tissues). Similar to TACE, this is a procedure in which an interventional radiologist selectively injects the artery or arteries supplying the tumor with a chemotherapeutic agent. No studies have been done to compare whether SIRT is superior to TACE in terms of survival outcomes, although retrospective studies suggest similar efficacy [58].

Intra-arterial iodine-131- lipiodol administration efficacy demonstrated in unresectable patients those with portal vein thrombus. This treatment is also used as adjuvant therapy in resected patients(Lau at al,1999),It is believed to raise the 3-year survival rate from 46% to 86%.This adjuvant therapy is in phase 111 clinical trials in Singapore and is available as a standard medical treatment to qualified patients in Hong Kong[59].

Percutaneous ethanol injection (PEI) well tolerated, high RR in small (<3cm) solitary tumors, as of 2005, no randomized trial comparing resection to percutaneous treatments, recurrence rates similar to those for post -resection.However a comparative study found that local therapy can achieve a five year survival rate around 60% for patients with HCC[60].

Combined PEI and TACE and Portal vein Embolization(PVE).Combined PEI and TACE can be used for tumors larger than 4 cm in diameter, although some Italian groups have had success with larger tumors using TACE alone.PVE using a percutaneous trans hepatic approach, an interventional radiologist embolisms the portal vein supplying the side of the liver with tumor. Compensatory hypertrophy of the surviving lobe can qualify the patient for resection. This

procedure can also serve as a bridge to transplant [61].

Complications: The most common complications of both TACE and SIRT is post embolization syndrome occurring in 60-80% of patients in TACE and 20-55% in SIRT[62].

Adjuvant therapy: A single trial showed decrease in new tumors in patients receiving oral synthetic retinoid for 12 months after resection/ablation; results not reproduced. Clinical trials have varying results [63].

VII. Prognosis and Prevention

Prognosis: The usual outcome is poor, because only 10-20% of HCC can be removed completely using surgery. If the cancer cannot be completely removed, the disease is usually deadly within 3 to 6 months[64].This is partially due to late presentation with large tumors, but also the lack of medical expertise and facilities in the regions with high HCC prevalence. However, survival can vary, and occasionally people will survive longer than 6 months.The prognosis for metastatic or unrespectable HCC has recently improved due to the approval of sorafenib(Nexavar®) for advanced HCC[64].

Prevention:Since hepatitis B or C is one of the main causes of HCC prevention of this infection is key to then prevent HCC. Thus, childhood vaccination against hepatitis B may reduce the risk of liver cancer in the future [65].In the case of patients with cirrhosis, alcohol consumption is to be avoided. Also screening for hemochromatosis may be beneficial for some patients [66].**It is unclear if screening those with chronic liver disease for hepatocellular carcinoma improves outcomes [67].**

VIII. Conclusion

Hepatocellular carcinoma(HCC) have high prevalence and mortality in Asia and Africa. The gold standard of controlling HCC by decreasing the incidence of HBV-related chronic liver disease cirrhosis and HCC, by infant HB vaccination.

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