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Hepatocellular carcinoma: Review of the literature

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Abstract

Hepatocellular carcinoma is the most common primary liver malignancy. Risk factors as viral infection, obesity, excessive alcohol use, and tobacco use are associated with the development of hepatocellular carcinoma. Hepatocellular carcinoma presentation ranges from asymptomatic to upper abdominal pain along with lethargy, weight loss, nausea, and anorexia. Different staging systems has developed in the past to stage hepatocellular carcinoma. Many treatment approaches have been used for HCC including chemotherapy, immunotherapy, ablation therapy, surgery, and liver transplantation.

Keywords: Hepatocellular carcinoma; Risk factors; Staging; Prevention; Treatment

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and is steadily growing to become the leading cause of cancer mortality. It usually presents in patients with a history of liver disease. Patients with HCC can be asymptomatic on diagnosis or can present with symptoms such as abdominal pain, fever, weight loss, and anorexia. Diagnosing HCC can be done through imaging, biomarkers, and liver biopsy. Staging of the HCC tumor is important in order to determine the most effective treatment for the patient. Many treatment options are available for HCC including chemotherapy, radiation, ablation, and liver transplant.

2. Epidemiology

There are different types of primary liver cancer including hepatocellular carcinoma, intrahepatic cholangiocarcinoma, angiocarcinoma, hepatic adenoma, and hemangioma. Primary liver cancer is considered to be the seventh most common cause of cancer worldwide, and the second leading cause of cancer mortality [1]. The most prominent type of primary liver cancer is hepatocellular carcinoma (HCC), estimated to comprise 75% of all primary liver cancers [1]. Hepatocellular carcinoma (HCC) is the sixth highest cause of cancer incidence and the fourth leading cause of cancer-related death worldwide [2]. In the United States, HCC is shown to be the most rising cause of cancer-related death, as well as the most recurrent hepatic malignancy [3, 4]. When it comes to gender, men have a fourfold higher rate than women to develop HCC [1]. In addition, age is positively correlated with the incidence of developing HCC [1]. HCC is found in certain geographic locations more than others. For instance, it is estimated that 72% of HCC cases occur in Asia, mainly in China, followed by Europe with 10%, while only 5% of cases occur in North America [5]. In the United States, the incidence of HCC is highest among the American Indian/Alaskan native population, followed by Hispanic population, followed by Non-Hispanic black population, and least incidence of HCC is found among Non-Hispanic white population [6]. Hepatitis B virus (HBV) and Hepatitis C virus (HCV) are the two main risk factors of HCC, with HBV being the most

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common underlying etiology of HCC worldwide, while HCV is responsible for the majority of cases in western countries [7]. Nonalcoholic steatohepatitis (NASH) has become a major cause of HCC with the prevalence of HCC related to NASH increasing [2, 8]. HCC related to NASH is the second leading cause of liver transplant in the United States. NASH is associated with obesity and type 2 diabetes mellitus (T2DM), and the most prevalent cancer in people with obesity and T2DM is HCC [2]. The death toll caused by HCC is quite high, and in 2018, it was estimated that a total of 810,000 people died from HCC [8]. Based on 2021 data from the World Health Organization, HCC mortality is on the rise in northern Europe and North America, while is declining in traditionally high-risk places including the Mediterranean, Japan and China [7].

3. Risk Factors

The main cause of HCC worldwide is a chronic infection with either hepatitis B virus or hepatitis C virus. Hepatitis D virus (HDV) is another important player that is shown to enhance cancer risk in HBV carriers [10]. HCC risk in individuals with HBV and HCV is related mainly to the stage of the liver disease with the risk of HCC gradually increasing as liver fibrosis progresses. HBV is known to be the strongest epidemiologic factor associated with HCC and studies have shown that HBV infected patients have up to a 20-fold increased risk for development of HCC compared to non-infected individuals [7,11,12]. Specific populations of HBV carriers are more susceptible to developing HCC, including individuals that are male, older, smokers, have high alcohol intake, as well as with history of T2DM and higher BMI [7]. HBV specific genome, both viral level and

HBV antigen level are positively correlated with increased risk of developing HCC [7]. HCV is similar to HBV in terms of patients with established HCV infection having up to 20-fold increased risk of developing HCC compared to non-infected individuals [13]. In addition, the annual incidence of HCC in HCV patients increases from 1% to 7% once cirrhosis is established in patients with HCV [14].

Table 1 Risk Factors associated with development of HCC

Hepatitis B infection
Hepatitis C infection
Metabolic syndrome
Obesity
Type two diabetes mellitus
Non-alcoholic fatty liver disease (NAFLD)
Excessive alcohol consumption
Tobacco use
AFB-1 toxin
Genetic mutations

Other than viral infections, many other risk factors such as metabolic syndrome, obesity, T2DM and non-alcoholic fatty liver disease (NAFLD) are associated with a higher risk of developing HCC in the future [15.16]. Excessive consumption of alcohol is an additional risk factor for developing HCC [17]. Active and former cigarette smoking individuals have a higher risk of developing liver cancer [18]. Exposure to AFB-1 toxin increases the risk of developing HCC by 6-fold and the risk of developing HCC will increase by 54-fold if a patient has HBV infection and exposure to AFB-1 [19]. Multiple studies have shown that increased iron intake will increase the risk of developing HCC [20]. Lastly, genetic mutations especially in the genes for hemochromatosis, alpha 1-antitrypsin deficiency, glycogen storage diseases and Wilson disease increase susceptibility to the development of HCC.

4. Protective Agents Against Developing HCC

Several agents have been associated and labeled as protective agents against the development of HCC. Coffee was found to be one such protective agent against development of HCC [21]. The mechanism of how coffee protects against development of HCC remains unclear, but one of the hypotheses is that polyphenols, which is an antioxidant that is found in coffee, protects against oxidative stress that causes damage to DNA molecules [22]. Caffeine found in coffee

also decreases cell proliferation, which in turn enhances protection against development of HCC [23]. A recent study demonstrated that consuming coffee will lead to less recurrence of HCC after liver transplantation, as well longer survival following orthotopic liver transplantation [24]. A large study that was done from 1988-1999 and included at total of 110,792 individuals, showed that patients with HCC who consume one cup of coffee a day have a lower mortality rate compared to patients with HCC that don't consume coffee daily [25]. In addition, a recent study showed that increased tea intake is associated with lower risk of developing HCC [26]. Adherence to Mediterranean diet is reported to be protective against HCC development in several studies [27]. More specifically, consuming vegetables, fruits and white meat have shown to lower the risk of developing HCC. On the other hand, consuming processed meat, red meat, sugar sweetened beverages and higher dairy intake are associated with a higher risk of developing HCC [27,28,29,30,31]. Lastly, estrogen has also been found to have a protective role against development and progression of HCC [32].

5. Presentation and Diagnosing

Hepatocellular carcinoma presentation ranges from asymptomatic to upper abdominal pain along with lethargy, weight loss, nausea, and anorexia. Once a tumor is in advanced stages, patients can present with severe right upper quadrant abdominal pain, persistent fever, as well as with findings of hepatomegaly and obstructive jaundice on physical exam [33].

Ultrasonography (US), contrast enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are usually used for diagnosing, treatment, management and monitoring progression of HCC [34]. Contrast enhanced CT and MRI scans are used for analyzing diverse liver nodules and are able to characterize late stage of HCC by its exclusive appearance of arterial phase vascularity [35]. Confirming the diagnoses of HCC or monitoring the progression of a liver nodule further depend on guidelines that is still debatable. For example, the European association of the study of the liver reports no need for liver biopsy to confirm HCC if the patient is presenting with a lesion >2 cm along with AFP >400 ng/ml [36]. The American association for the study of liver disease recommends that any liver lesion smaller than 1 cm needs to be reexamined twice a year and if there are no radiological changes over two years, then routine surveillance guidelines should be followed [37]. Asian pacific association for the study of liver recommend that every liver nodule with uncharacteristic vascular profile should undergo further imaging, such as endoscopic ultrasonography (EUS) to rule in or out HCC [38]. New imaging studies are on the rise that may be more sensitive and specific to in diagnosing HCC. Diffusion weighted imaging (DWI) is an up and coming technique that can be used to diagnose liver lesions safely for patients who are allergic to contrast media. However, it cannot precisely differentiate between HCC and dysplastic nodules, or other malignant and benign lesions [39].

Table 2 Biomarkers associated with HCC

Alfa Fetoprotein (AFP)
Alfa Fetoprotein-L3
Des-gamma-carboxy prothrombin
Trefoil factor 3

Serological biomarkers are used to aid in the diagnosis of HCC. Alpha Fetoprotein (AFP) is used extensively for determination of HCC. The sensitivity of AFP ranges from 25% for nodules smaller than 3 cm, to 50% for lesions larger than 3 cm in diameter [40]. However, AFP level can vary depending on the patient's stage of cirrhosis. AFP is also found in germ cell tumors, gastric cancer and chronic liver disease; therefore, it cannot be used solely to diagnose HCC [19]. AFP has a higher sensitivity and low specificity, or vice versa, depending on how high or low it measures. For example, AFP cut-off above 30 ng/ml will have an excellent sensitivity but poor specificity, while AFP cut-off below 2000 will have a poor sensitivity and an excellent specificity. AFP-L3 is a glycoform of AFP that originates from cancer cells and demonstrates higher specificity for HCC [41]. Des-gamma-carboxy prothrombin (DCP) is an abnormal prothrombin molecule that is induced by the absence of vitamin K or antagonist II, and is shown to have a sensitivity and specificity of 77% and 82%, respectively, for early diagnosis of HCC [42]. Recent studies haven't demonstrated any benefit of using DCP over AFP; therefore, it hasn't been used widely [43]. The combination of AFP, AFP-L3 and DCP markers to identify HCC earlier has been showing promising results, but no new algorithm that contains all three markers has been used in western guidelines yet and more studies are required to establish one [44]. Other than AFP, AFP-L3, and DCP, a secretory protein called Trefoil factor 3 (TFF3) has been found to be highly expressed in the tissues of HCC and has the potential to become a serum marker for diagnosing HCC [45]. The presence of hypermethylated DNA, especially in the

CpG domain, has been associated with the progression of HCC and studies have shown that it might also become a highly sensitive noninvasive test that could be used for early detection of HCC in the future [46].

6. Staging

Hepatocellular carcinoma is a worldwide burden and many staging systems have been developed in the recent years, but not a single system has been universally accepted as of yet. Each staging system offers some benefits, but also comes with limitations as well. One of the most adopted staging systems is the Barcelona clinic liver cancer (BCLC) classification which was proposed in 1999 by Llovet et al. The BCLC has been accepted by many associations, including the American gastroenterology association [47]. The benefit of BCLC is that it includes predictors of prognosis in HCC patients such as tumor extension, liver function and the overall physical status of the patient [48]. In addition, it was the first system that provided evidence-based clinical treatments for each patient with HCC depending on the individual different stages of the patient's tumor [48]. Another staging system that was popular in the past is the Okuda score that originated in 1985 [49]. It combined tumor size, along with variables such as ascites, serum albumin, and bilirubin level, to separate patients with HCC into 3 stages: not advanced, moderately advanced and very advanced [49]. The main reason for the popularity of that system was the simplicity of staging that the system provided, although in comparison to BCLC, it was limited due to the inability to provide a treatment plan, as well didn't taking into consideration the patient's overall health considering their staging. The American joint committee of cancer has been using the Vauthey et al staging system that takes into account the TNM staging and addresses independent predictors of mortality, such as vascular invasion and severe fibrotic cirrhosis [50]. The main limitation of the Vauthey staging system is that it does not take liver function into account [51]. In Japan, the Japan integrated staging score (JIS score) is being utilized for patients with HCC. It was proposed by Kudo et al in 2003 and is a combination of the LCSGJ staging score along with evaluation of patient liver function [52]. It has been found to be superior in prognostic determination compared to BCLC and CLIP staging scores, but the main limitation is that it was solely developed for Japanese patients [53]. Other systems that have been developed in the past include HKLC, MESSIAH, Tokyo, CUPI, ALPCS, and Hong Kong liver cancer classification [48].

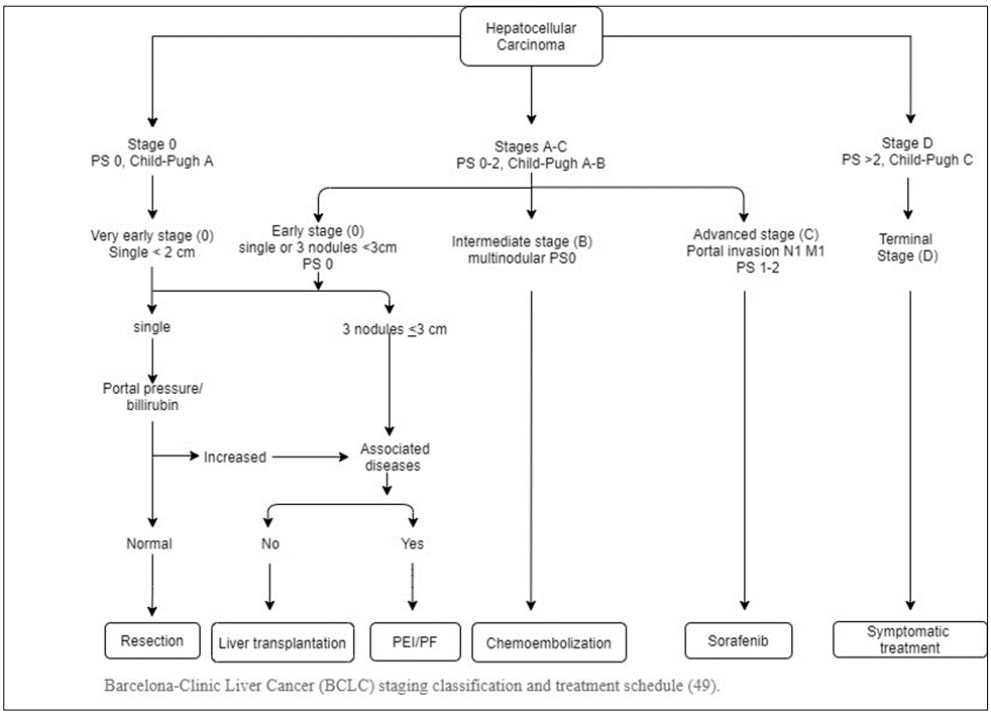

Figure 1 Barcelona-Clinic Liver Cancer staging system

7. Treatment

Due to the complexity and poor prognosis of hepatocellular carcinoma, the optimal therapeutic approach is individualized for each patient and usually determined by a multidisciplinary team composed of hepatologist, surgeon, oncologist, radiologist and pathologist [54]. Many treatment approaches have been used for HCC including

chemotherapy, immunotherapy, ablation therapy, surgery, and liver transplantation. Despite the various treatment options available, the overall prognosis for HCC is still poor with a 5-year survival rate at approximately 5%-30% [55].

Surgical approach for HCC is still regarded as the first-choice treatment [56]. Laparoscopic hepatectomy has been shown to be less invasive then open surgical hepatectomy and has been a promising approach for treating patients with HCC [56]. Patients who are non-cirrhotic with an appropriate staged HCC will benefit the most from hepatic resection with minimal morbidity [57]. Given that, only 30-40% of patients with HCC will qualify for surgical approach as an option [58]. While surgery is regarded as the mainstay of treatment for HCC, high tumor burden and patients with decompensated liver function will make surgery an unfeasible option. These patients may benefit from other approaches, such as immunotherapy and ablation therapy [59].

Transarterial chemoembolization (TACE) is the treatment of choice for patients with HCC who are deemed poor candidates for curative surgical treatment. Initially, TACE was introduced as palliative treatment in patients with unresectable HCC, but now TACE is not only the preferred treatment for unresectable HCC, but the only treatment for unresectable HCC larger than 10 cm in diameter [58]. It is also offered for patients who are awaiting liver transplant, or prior to radiofrequency ablation, also known as bridging therapy [60]. TACE is also the first-line treatment for patients with multinodular tumor that have well-preserved liver function with no evidence of vascular invasion or metastasis [61]. TACE works by blocking the hepatic artery blood flow to the site of the tumor, while delivering chemotherapy drugs to the tumor. Given that the liver tumor receives much of its supply from hepatic arteries, the rest of liver tissue receives blood supply from the portal vein. This enables oncologists to cut off the blood supply to the tumor without affecting the rest of the healthy liver tissue [62]. Patients who qualify for TACE treatment must have good liver function, no presence of ascites, and no prior problems with their portal vein. The main drugs that are commonly used in conjunction with TACE treatment are Doxorubicin, Cisplatin, and Mitomycin [62]. Recent research is being conducted to investigate whether intravenous Bevacizumab, which is anti-vascular endothelial growth factor (VEGF), is beneficial in treating patients with HCC who undergo TACE treatment. The concept is anti-VEGF will inhibit angiogenesis in the vascular structure of the tumor [58]. As of now, there are currently two ongoing trials evaluating the efficacy of using of bevacizumab in unresectable liver cancer [58]. TACE treatment has been shown to prolong survival and control the symptoms of HCC [58].

Immunotherapy is another exciting cancer treatment option that has been approved for use in Hodgkin lymphoma, melanoma bladder, non-small cell lung and renal cancer. The concept of immunotherapy arose from the theory that T-cell dysfunction plays a role in cancer pathophysiology. Immunotherapy focuses on stimulating T-cell production in patients with cancer in an attempt to try and correct the suspected T-cell dysfunction, this technique is referred to as vaccine therapy [55]. In order to activate T-cells against cancer cells, a specific antigen must be targeted. AFP has been shown to be a promising target antigen given its presence in HCC cells [59]. Another immunotherapy approach is to load the tumor antigen into presenting cells such as dendritic cells, activated B cells, and peripheral blood mononuclear cells [63]. This process enhances T-cell stimulation in order to generate potent CTLs. Lastly, immunotherapy involves adoptive cell therapy which expands certain cells such as CD8T cells ex vivo and then infuses the cells back into patients at the site of the tumor to mediate its destruction [64].

Ablation therapy is another approach for patients with HCC that mainly targets early stages of the disease, as well as HCC limited to the liver with no extra hepatic metastasis [54]. The two main types of ablation therapy that are used for HCC patients are percutaneous ethanol injection and radiofrequency ablation therapy. Percutaneous ethanol injection (PEI) is a treatment used for nodular HCC by injecting ethanol intra-lesion by using non-cutting needles over multiple sessions that can be done in an outpatient setting. HCC tumors smaller than 2 cm have been shown to have the best results from PEI, whereas bigger tumors are more challenging to treat with PEI [54]. Major complications with PEI include intraperitoneal hemorrhage, liver failure, biliary fistula and renal failure [65]. Percutaneous radiofrequency ablation (RFA) is the most common used procedure in patients with HCC due to its higher efficacy and safety profile. Radiofrequency ablation (RFA) is a thermal ablation obtained by generating a large amount of friction heat leading to irreversible cellular damage. Contraindications for RFA treatment include if the location of the tumor is at the dome or inferior edge of the liver due to risk of diaphragmatic injury [66]. In addition, patients with Child Pugh C, patients presenting with altered mental status or have an active infection are not candidates for RFA therapy [66]. RFA has been shown to be more favorable than EPI due to the fact that it requires fewer sessions as well as better outcomes in terms of eradication of disease [67]. In addition, local recurrence of HCC tumors in patients who undergo RFA treatment has been significantly lower in comparison to patients who undergo PEI treatment.

Liver transplant comes the closest to a cure for treating patients with HCC. It offers a complete resection of the tumor; however, recurrence rates remain high. In addition, the demands for liver transplants far exceeds the available supply [60]. For this reason, specific criteria must be met in order for a patients with HCC to qualify for liver transplant. MILAN

criteria models have been developed in the past to recognize patients with HCC that qualify for liver transplant [64]. Candidates must have a solitary tumor of <5 cm in diameter, or up to three tumor nodules with each one measureing <3 cm in diameter [64].

8. Conclusion

Hepatocellular carcinoma is a primary liver malignancy that is one of the leading causes of cancer related mortality. Presentation of the tumor can be vague and patients with history of liver disease need to be monitored closely in order to diagnose HCC at early stages. Many treatment options are available for HCC, but the tumor needs to be staged correctly in order to choose the most appropriate treatment. Overall, HCC is a complex malignancy and patients will need to follow-up closely with a hepatologist to ensure prompt diagnosis and staging, and ensure the correct treatment option is utilized to prevent complications and have the greatest chance for recovery.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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