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REVIEW ARTICLE

Hepatocellular carcinoma: An update of risk factors, staging and treatment

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Abstract

Hepatocellular carcinoma (HCC) is the 5th most frequent death cause in the world. Numerous risk factors provoke HCC progress including aflatoxins, chronic alcohol consumption, HBV, HCV, porphyria's and even contraceptives. Early stage diagnosis and treatment of HCC is still a dilemma. Several invasive and non-invasive techniques are frequently used for its detection. Different biomarkers are also used for early diagnosis of HCC. HCC has been categorized into several stages depending upon the nature of tumor. Several treatment strategies are used for HCC including the surgical and non-surgical methods. Surgical methods are liver transplant and surgical resection while non-surgical are ablation, percutaneous ablation, laser thermal ablation, radiofrequency ablation, trans-arterial chemoembolization, hormonal therapy and chemotherapy. This review is focused on multiple risk factors of HCC, disease epidemiology in different countries, different staging systems used for diagnosis and various treatment interventions including surgical and non-surgical for HCC treatment.

Keywords

Diagnosis
Hepatocellular carcinoma
Risk factors
Staging system
Treatment

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Introduction

Among different types of cancers hepatocellular carcinoma is fifth most frequent cancer type worldwide and the third major death cause (Ferlay et al., 2010). Cirrhotic liver may further leads to the liver cancer (Gomaa et al., 2014). Hepatocellular carcinoma can be diagnosed earlier now due to advancements in technology. It is possible to treat patients with different treatment opportunities if disease is diagnosed at earlier stages (Salhab & Canelo, 2011). Various treatments are being used in case of early stage diagnosis including radiofrequency ablation, percutaneous ethanol injection, radio embolization and surgical resection (Karaman et al., 2014). About 100,000 cases of hepatocellular carcinoma have been reported each year in UK, Europe and Australia. Men are at higher risk of HCC then women (Nguyen & Thuluvath, 2008). The lungs, abdominal lymph node, diaphragm and bones are the most commonly affected extra hepatic sites. However, metastasis to the oral cavity is particularly intermittent and rarely encountered. HCC remains a malignant disease which in most cases leads to death. Better understanding of molecular and histological aspects should be made in order to treat and diagnose HCC at early stages (Waly Raphael et al., 2012). Although HCC occurred in cirrhotic liver but according to some studies about 20% cases occurred in non-cirrhotic liver. An understanding of this feature must be considered in order to prevent false diagnosis (Trevisani et al., 2010). In order to decrease the mortality and morbidity of HCC, early diagnosis and the expansion of novel systemic therapies for advanced disease, including gene, drug and immune

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therapies as well as primary HCC prevention are of great importance (Blum, 2005).

Epidemiology: The highest number of cases prevail in Asia and Africa which were approximately 85% (Altekruse et al., 2009).The areas which were reported with less number of cases of HCC are Northern Europe, South and North America. The cases reported were higher in male as compared to in female but according to a report in areas of Zimbabwe, Colombia, Costa Rica, South Karachi and Pakistan, chances are equal in both genders. The reason is not clear that why male are more susceptible but it may be due to sex specific prevalence of risk factors. Male are likely to get infected by hepatitis A and & B virus because they consume alcohol, cigarette smoking and iron store is more as compared to female. Level of aflatoxins are also higher in male as compared to female. Incidence rate may also differ according to race and ethnicity. According to a report from USA it was found that rate of HCC occurrence was higher in Asian as comparison to the White. During the era of 1983-1987 and 1998-2002, HCC cases increased in many areas especially in India, Northern Europe, Israel, North and South America. While, at the same time rate of incidence decreased in Spain and East Asian countries (McGlynn & London, 2011).

HCC is the third most fatal cancer resulting in over 500,000 deaths per year. In the United States, HCC is the eighth most usual reason of cancer related deaths rendering 8.5 deaths per 100,000 (Amit, 2008). The chances of HCC in the US has increased to 4.1 per 100,000 from 1.6 per 100,000 in the last 20 to 30 years (Atla et al., 2012). The occurrence of hepatocellular carcinoma (HCC) has become doubled in the United States from 1983 to 2002 (Ascha et al., 2010).

Risk factors: About 75-80% of HCC occurrence are due to HBV and about 10-15% is due to HCV. Other risk factors are excessive alcohol intake, aflatoxins, diabetes, some rare metabolic disorders, hemochromatosis and many porphyrias (Mimi & Yuan, 2004). Hepatocellular carcinoma risk is lower in HBV immune people (Wu et al., 2007) (Ayub et al., 2013). Prosperous antiviral therapy in HCV patients linked to cirrhosis may deteriorate HCC risk somewhat amongst patients treated with interferon but is poorly documented since studies are mostly from non-randomized and observational clinical trials (Tu et al., 2009).

Chronic excessive intake of alcohol is key risk factor of HCC. Cirrhosis may be developed with continuous intake of large amount of alcohol. Risk is increased by two folds when effect of alcohol is synergized with HBV or HCV (Karim et al., 2012) (Donato et al., 2002).

Aflatoxins, another risk factor, are mycotoxin produced by fungus. They are a strong hepatocarcinogens. Once ingested, it is converted to an inactive intermediate which binds with DNA and produce damage and mutations. Obesity is another risk factor. Insulin resistance may leads to steatosis causing an increased necro-inflammatory activity and hence leading to fibrosis. As a result of these, liver diseases and metabolism disturbances may occur which sometimes may also leads to HCC (Castaldo & Pinson, 2007).

Oral contraceptives may be another cause of HCC. In hepatocytes, nuclear estrogen receptors are present and their level increased in case of HCC. Estrogen and progesterone may cause an increased risk of HCC. Estrogen may cause neoplasia of liver leading to mutation (Calle et al., 2003). Three cohort studies have stated the link between HCC risk and coffee intake. Among those, 2 studies exhibited a marked decrease in HCC risk with coffee intake of one or more coffee cups while the second study showed a dose response. Another study presented a reduced HCC chances with coffee drinking of average significance (El–Serag & Rudolph, 2007). Smoking is also a major cause of hepatocellular carcinoma (Koh et al., 2011) (Lau, 2003). Instead of environmental, viral, behavioral and metabolic characteristics, inherited factors have also been seen to explain the different chances to develop HCC. Chances of death from HCC are more in White American people as compared to black people (Sloane et al., 2006).

Staging system in HCC: Staging system is usually used to select suitable therapy for determination of prognosis and it also helps in evaluation of results obtained from treatment. At the moment, experts describe eight staging system for HCC (Vauthey et al., 2002). But there is no universal acceptance for any of them. Three among the eight stages has been validated in different patients while there is no clear system for other four stages. So a proper staging classification is required for HCC (Bruix & Sherman, 2011). Most cancers of human body can be staged on the basic of tumor size, tumor using distant metastasis, invasion of lymphatic system and the nodes and metastasis staging system (Sarwar et al., 2015).

Okuda classification has been used in last ten years in HCC patients. It includes different parameters related to liver such as ascites, billirubin and albumin. The Okuda system was developed about 20 years ago based on data from HCC patients at advanced stages (Cammà & Cabibbo, 2009). This classification is more satisfactory as patients were diagnosed at early stages (Minagawa et al., 2007). But now a days this classification does not seem to be satisfactory because when it was compared with latest staging systems it is found to be of low predictive capacity (Waller et al., 2015).

French classification was constructed when 761 patients of hepatocellular carcinoma were analyzed and 47% patient among them received specific treatment. On comparison of this system with modern systems it was found that in patients with HCC at early stages it has limited prognostic capacity.

CLIP Score the cancer of liver Italian program score was formed by retrospective studies. It has been compared with TNM and Okuda stage with better power of discernment (Zhao et al., 2002). From the facts it was also said that it does not serve to provide suitable therapy for each patient (André et al., 2004). The CLIP scoring system was obtained from a retrospective analysis of 435 patients with HCC from 16 Italian institutions and was published in 1998 (Marrero et al., 2010).

Barcelona clinic liver cancer staging system was formed by the several results obtained from many cohort studies. But this is not a scoring method as it was obtained from the identification of many independent prognostic factors. This system of classification included the status related to physical, functional status and cancer related symptoms (Zhao et al., 2015). It encompassed various stages the e.g. patient at stage A should undergo radical therapy which may include transplantation of liver, resection or percutaneous treatment. Patients who were at stage B should undergo chemoembolization. At stage C patient may receive new agents while at stage D patient would receive symptomatic treatment. So it might be considered as best system for staging in patients at early stages of HCC (Pons et al., 2005).

CUPI (Chinese University Prognostic Index) considered six variables which were predictive and then they divided the patients into three stages. This classification was found to be the most effective one as compared to Okuda and CLIP score method.

TNM stage is the system which only included the variables related to tumor stage. It showed poor prognostic prediction in patient suffering from HCC and undergoing transplantation or resection. It is still under discussion that whether to use this system of staging for non surgical patients or not.

JIS staging is Japan Integrated Staging which included two systems of classification one is TNM classification and other is Child Pugh classification but external validation was still at lack in western countries.

Diagnosis: Diagnosis of HCC involves a series of invasive and non-invasive tests along with various biomarkers for adequate diagnosis.

First of all when nodule has been detected in liver its characterization and detection should be done because HCC has a particular vascular profile in which arterial vascularization has been viewed (Page et al., 2014). So it might be concluded that it is possible to diagnose HCC without any histological examination with the help of results obtained from dynamic imaging techniques of the specific vascular pattern. When nodule in the liver is of greater then 2cm size, then it might be diagnosed as HCC requiring no biopsy but when vascular pattern is not clear, biopsy would be needed. If any hepatic nodule is detected along with increase in level of alpha fetoproteins above 200 ng/dl , it might also be diagnosed as HCC (Gomaa et al., 2009). Dynamic imaging techniques probably be the best option for diagnosis. Results would be more accurate if the nodule detected along with the use of dynamic imaging technique. Level of alpha fetoproteins might not be considered as standard because in some patients with the diagnosis of HCC, the level of alpha fetoproteins has been found to be normal (Forner et al., 2006).

Des gamma carboxyprothrombin is a tumor marker for HCC diagnosis. Along with this some other markers can also be used which may includes urinary tumor growth factor-ß1 and interleukin-2. Ultrasound may also be performed for the diagnosis of HCC (Wong et al., 2000). CT is better alternate of ultrasound (Caturelli et al., 2002). Spiral technique should be used for using CT which includes intravenous injection of contrast and images would be obtained at portal, arterial, basal and equilibrium phases. First of all uptake of contrast is done in the arterial phase. Hypervascularization of small tumor occurs due to which efficacy of CT decreased for the tumor of size less then 2cm. So for detection of tumor of size less then 2cm spiral technique being used. It may give more accurate results than normal CT (França et al., 2004).

Magnetic resonance imaging technique is also used for the diagnosis of HCC. It may lead to the identification of lesions present in liver. Sensitivity of MRI is less for tumor of size 52cm in diameter. Sensitivity can be enhanced by using supramagnetic iron oxide contrast comprising of tissue specific MRI contrast agent particles which are taken up by liver (Benvegnu et al., 2004).

Angiography has also been used as diagnostic tool because of its highly vascular nature but it did not work for the tumor of size of 52cm in diameter (Vauthey et al., 2010). Now a days angiography is used for the detection of liver anatomy before any sort of surgery. Sometimes liver biopsy may also be done for diagnosis of HCC (Kudo et al., 2004). Percutaneous fine needle aspiration is usually done in order to obtain histological and cytological samples. Core biopsy method may also be used. The two methods collectively may provide better results. When HCC lesions cannot be located precisely by radiographic method, open surgical biopsy processes may be performed. Microscopically the observed features are atypical naked nuclei, increased nuclear to cytoplasmic ratio and peripheral endothelial wrapping. Histologic manifestations range from about normal appearing hepatocytes in well differentiated tumors to the largely anaplastic multinucleate giant cells (Bialecki & Di Bisceglie, 2005).

Biomarkers for diagnosis: As cancer is deregulation of gene expression so is very hard to differentiate between the tumors which are similar morphologically

but differ from each other at molecular level when assessed pathologically. It is necessary to find some non-invasive biomarker to monitor molecular difference in tumor (Kosaka et al., 2010). More than 60% of patients who are suffering with hepatocellular carcinoma do not receive proper curative therapy as a consequence of late diagnosis and clinical presentation.

Plasma mRNA have been identified for the treatment of hepatocellular carcinoma related to hepatitis B. This method of diagnosis fall into two main categories i.e. biomarker test and imaging. It has been found that miR-122, miR-192, miR-223, miR-801 and miR-27a are the markers which are potentially circulating for the diagnosis of HCC. Among them miR-122 is the most commonly found micro RNA in the liver. On the other hand miR-27a found to be an oncogene in gastric cancer. Panel of plasma micro RNA are involved which may cause differentiation of hepatocellular carcinoma from healthy and cirrhotic cases with high chances of accuracy (Zhou et al., 2011).

From studies it has also found that VEGF and Ang2 are the independent and strong predicators for survival of patients with hepatocellular carcinoma. These two biomarkers may derive angiogenesis hence enable the growth and metastasis of hepatocellular carcinoma. High level of Ang2 in plasma are the indicators of poor prognosis of patients with HCC. Increased level of Ang2 may suggest that angiogenic factor might be associated with some other destructive disease (Llovet et al., 2012).

Treatments

Surgical treatment

Liver transplant: Among various treatments used for hepatocellular carcinoma, liver transplant is mostly recommended (El-Serag et al., 2008). However high recurrence rate and poor outcome was observed in 1980's in the patients with liver transplantation (Belghiti & Kianmanesh, 2005). The factors which might be responsible for these are involvement of lymph node, extrahepatic spread at the time of procedure and microscopic vascular invasion (Chen et al., 2014). Due to these factor once the procedure was not well appreciated but in 1990's new era of liver transplantation started. Investigation of the earlier practice recommended that patients with minute or incidental asymptomatic tumors revealed at the time of transplantation (Hshieh & Sundaram, 2013). Information of only vascular invasion or its surrogate markers such as degree of poor differentiation are able to change the diagnosis of candidates by causing recurrence in a minority of patients (Cabrera & Nelson, 2010).

Now a days a new condition is faced, with two opposite driving forces in the field. First, proof that the less number of donors has led to really long waiting times in almost all countries has unclear the outcomes reported when analyzed according to objective to treat (Shi et al., 2010). First, adjuvant therapies percutaneous ablation, chemoembolization or even chemotherapy during the time on the waiting list have been used. Second, increasing numbers of studies are proposing that the development of the conventional criteria may not adversely impact survival (Bruix & Sherman, 2005). Liver transplantation is more common in white as compared to Asian people (Xu et al., 2016).

Surgical resection: It is mostly used for treatment of HCC. Transplantation and resection are the main processes used as treatment of HCC. Resection produce good results in patients who present with excellent liver functional reserve and single tumor (Schwartz et al., 2002). Portal hypertension is usually related to these conditions(Ng et al., 2009). Adjuvant therapies like chemotherapy or chemoembolization may not produce satisfactory results while on the other hand treatment with interferon might produce significant results (Llovet, 2005). Resection would be considered as the first line treatment with patient who have isolated tumor which was limited to liver only (Poon & Fan, 2004). Many surgeons restrict the use of resection in the patients who have the tumor of size more than 5cm or may be smaller than this, although there are no general rules for selecting patients for resection even if chances of vascular lesion increased with increase in tumor size (Crissien & Frenette, 2014).

Non-surgical treatment for HCC: Some non-surgical techniques may also be used for the treatment of hepatocellular carcinoma.

Ablation technique is a non-surgical method used for the treatment of HCC. This technique might be used in combination with liver resection or alone.

Percutaneous ethanol injection is another non-surgical remedy for HCC. This process was used earlier. This procedure is low in cost with need to be done repeatedly along with the greater chances of recurrence. An ethanol injection of (95%) is mostly used which may produce necrosis of tumor and may cause its shrinkage. Tissue ischemia and microvasculature thrombosis may occur which increased the chances of survival (Johnson, 2005).

Radiofrequency ablation (RFA) is another non-surgical procedure involving confined application of radiofrequency thermal energy to the abrasion is done in which a high frequency leading the electrode tip into the adjoining tissue. Necrosis occurs as the tissue temperature increases greater 60°C. This procedure might be done by surgical, laparoscopic or percutaneous techniques. However, RFA has a reduced recurrence rate as compared to ethanol injection in HCC patients having cirrhosis (Teratani et al., 2006).

Laser thermal ablation is another method done with the help of laser. Five watt laser joined to one to four fibers, focused percutaneously into the liver via 21 gauge needle. Tumors are treated for 6 to 12 minutes per session.

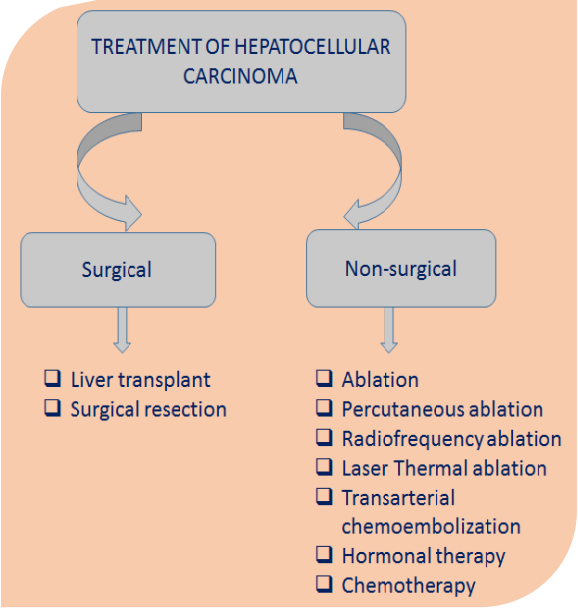

Figure 1: Surgical and non-surgical treatments of hepatocellular carcinoma

Transarterial chemoembolization is a chemotherapeutic agent injection used alone or in combination with procoagulant or lipiodol material into the hepatic artery. Lipoidal is contrast agent of oily nature that enhances intra tumoral retention of chemotherapeutic drugs (Kennedy & Sangro, 2014).

Hormonal therapy Several hormones have been studied in patients with advanced HCC including megestrol, tamoxifen, lanreotide and octreotide.

Laser ablation Laser ablation should be used for ablation with light energy applied through fibers directly inserted into the tissue. A huge variety of laser wavelengths and source are available. In addition to these different types of laser fibers, modified tips and single or multiple laser applicators are used (Crocetti & Lencioni, 2008).

Chemotherapy: Chemotherapy is also being used for the treatment of hepatocellular carcinoma. Among various agents used doxorubicin based doses seemed to have greatest efficacy with minimal effect on survival (Mendizabal & Reddy, 2009).Various biological and hormonal agents are also used including antiandrogens such as ketoconazole and cyproterone, tamoxifen, interleukin and interferon. Combination of oxaliplatin and gemcitabine are also being used for treatment of HCC. Sorafenib,a novel molecularly targeting drug, is approved by FDA for HCC treatment. It is used orally and found to have proapoptic and antiangiogenic properties. Sorafenib is different in its functions as it has potential to target many pathways by blocking RAF signaling pathway. In phase 3 clinical trials sorafenib found to be most effective (Bruix & Sherman, 2011). Bevacizumab in humanized cloned monoclonal antibody used for the treatment of HCC but its major side effect reported is bleeding. Bevacizumab has also been studied in combination with oxaliplatin and gemcitabine (GEMOX) for treatment of HCC (Olsen et al., 2010).

Conclusion: There is a strong need for improvement in the diagnostic techniques and treatment plans for hepatocellular carcinoma. Early diagnosis can limit the disease prognosis to a greater extent. Hence a very limited number of drugs are effective for treatment, so new treatment options must be explored. Molecularly targeted therapies are in different stages of clinical trials for approval of HCC treatment.

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