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Hepatocellular Carcinoma- A Review

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Abstract

Cancer is the most dangerous disease in the world because of its wide range of the morbidity and mortality. Cancer has become an important issue in medicine as it is major cause of death in both developed and developing countries. Among that, Hepatocellular carcinoma is a primary malignancy of the liver and it is the second leading cause of cancer- related deaths globally. The main risk factors for developing HCC are hepatitis B and C virus infection, alcohol intake and ingestion of fungal metabolite aflatoxin B_1. Additional risk factors are diabetes, non alcoholic fatty liver disease, and smoking. It has poor prognosis with a median survival time of approximately 11 months. The incidence of HCC is higher in men and in those over 40 years old. Early detection of HCC is critical to providing effective treatment which has a significant impact on survival. For that, understanding the carcinogenic process and staging system remains essential keys in diagnosis and treatment of HCC. This review outlines the minutiae of Hepatocellular carcinoma.

INTRODUCTION

Hepatocellular carcinoma is the most common primary hepatic malignancy with average survival rate between 6 to 20 months.[1] It is the fifth commonest malignancy and the second commonest global cause of cancer deaths.[2] Hepatocellular carcinoma is the fifth most common cancer in men and eighth most common cancer in women world wide resulting in at least 5,00,000 death per year.[3] The major cause of cancer is cirrhosis of liver due to alcohol abuse, autoimmune disease of liver, infection with hepatitis B and C virus, chronic inflammation of liver, Iron over load,[1-4] ingestion of fungal metabolite Aflatoxin B1, chemical and industrial carcinogens, metabolic syndrome, hepatovasular abnormalities [5] and diabetes.[6] Hepatocellular carcinoma has poor prognosis because of high rate of recurrence and liver failure.[7] More over two-thirds of Hepatocellular carcinoma patients are diagnosed at advanced stage even in developed countries.[2] Treatments such as hepatic resection and orthotopic liver transplant give good prognosis, but they are limited to early stage of Hepatocellular carcinoma. [8] Early diagnosis of the disease is very essential to improve the survival rate. For that, effective surveillance program and antiviral treatment for both hepatitis B and C are indispensable. [9]

Epidemiology

Hepatocellular carcinoma is diagnosed in more than half a million people world wide. The latest figure showed an estimated 7,48,300 new cases of HCC and 6,95,000 deaths caused by this disease. The World Health Organization (WHO) indicates HCC as the second leading cause of cancer- related death in humans due to its high incidence in the East, in areas of Africa, and in the Western Pacific.

In Asia-Pacific region especially north and South Korea, Indonesia and Vietnam, the rate of HCC in men is 4 folds higher than that of women. Approximately 85% of the cases occur in developing countries. The incidence of HCC is closely related to the incidence of HBV and HCV infection. [9-12] In Singapore, Japan and Australia, NewZealand, HCC is mainly due to high incidence of HCV infections. HCV infection is the main leading cause of HCC in Europe and United States. [13]

The prognosis of the liver cancer, even in developed countries is very unfavorable. In the United States the one year survival is less than 50% and the five year survival only 10%. Survival is even less favorable in developing countries. [12]

Etiopathogenesis

The primary risk factor or cause for developing HCC is cirrhosis. [14] There are varieties of congenital and acquired conditions, which induce the development of HCC without cirrhosis. They are viral hepatitis (HBV, HCV), Alcohol, Aflatoxin B1, Chemical and industrial carcinogens, Tissue Iron over load, inherited diseases, Metabolic syndrome, Hepatic vascular abnormalities, Benign tumours like hepatic adenoma and sex hormones. [15]

Cirrhosis of liver

Cirrhosis is the major risk factor for the HCC development. Most common causes of liver cirrhosis are chronic alcohol abuse, long term viral hepatitis C infection, hepatitis B infection, Non alcoholic fatty liver disease (NAFLD), and Non alcoholic steatohepatitis (NASH). Less common causes are auto immune hepatitis, damage to bile ducts, hemochromatosis, Wilson's disease and rare viral infections of liver like hepatitis D and hepatitis E and other causes are prolonged use of medications (like acetaminophen, some antibiotics, antidepressants), prolonged exposure to toxic chemicals, parasitic infections and chronic heart failure with liver congestion. [16] Thus chronic liver injury (cirrhosis) initiates increased liver cell turnover, triggering oxidative DNA damage and inflammatory events. This leads to formation of dysplastic and macro regenerative nodules which are considered to be neoplastic nodules. [17]

Hepatitis B virus

Hepatitis B Virus (HBV) is a partially double stranded circular DNA virus belonging to the hepadnavirus family. [18,19] HBV virions infect hepatocytes by binding to cellular surface receptors which remain unknown. Then the viral inner cores are transported into the nucleus where it is converted into covalently closed circular form DNA

(cccDNA) and it is transcribed into viral mRNA by the host RNA polymerase II. This mRNAs enter into the cytoplasm where they are translated into different viral proteins. Then, the viral inner cores are assembled in the cytoplasm. The inner core contains a single molecule of pregenomic RNA, a viral DNA polymerase and core proteins. The pregenomic DNA is then converted into double stranded DNA by reverse transcription. Most cores are then coated with viral lipoprotein envelopes by budding into the endoplasmic reticulum and they are exported from the cell as mature virions, while a small portion of core particles are transported back to the nucleus to maintain a stable pool. [20]

The major complication of Infection of HBV is HCC. Evolution of HCC may be the direct or the indirect effect of the virus. First, HBV infection causes hepatocytes injury and chronic necrotic inflammation with subsequent hepatocytes proliferation, fibrosis and cirrhosis. The continual necrosis of the hepatocytes during chronic HBV infection accompanied by rapid regeneration lead to accumulation of mutations in host genome which results in genetic alteration, chromosomal rearrangements, activation of the oncogenes and inactivation of the tumour suppressor genes. Finally it leads to HCC.

HBV can also cause HCC in absence of cirrhosis. In it, there is integration of HBV DNA in the host genome which may act as mutagenic agent or transactivation of oncogenes of the host by HBx protein or by another truncated protein derived from the pre-S_2/S region of HBV genome. HBV can integrate into genes encoding for proteins related control of cell signaling proliferation and viability, which leads to deregulation of the cell cycle control and interference with cellular DNA repair and apoptosis. [21-23]

Hepatitis C Virus

Hepatitis C Virus (HCV) is RNA virus belongs to the Hepacivirus genus, Flaviviridae family. HCV is transmitted mainly via blood and its products and other routes are occupational exposure, hemodialysis, household exposure, birth to an infected mother, intra nasal cocaine use, drug and sexual behavior. [24] After entering the susceptible host, HCV invades, infects and replicates within the bloodstream, peripheral B and T lymphocytes and various tissues like pancreas, thyroid, adrenal glands, spleen and bone marrow. Liver is the principal site of HCV replication. [25] HCV replicates in the cytoplasm of the hepatocytes. The replication ranging is between 10^{10}-10^{12} virions per day and the virions half life is 2-3 hour. Because of the rapid viral replication and lack of error proofreading by the viral RNA polymerase are reasons for HCV mutations. [26]

HCV can cause HCC by induction of chronic inflammation or by direct way via viral factors. In indirect way, HCV infection cause chronic hepatic inflammation, progressive liver fibrogensis, and initiation of neoplastic clones which leads to somatic genetic or epigenetic alterations and progression of malignant clones in a carcinogenic tissue microenvironment. [27]

In direct way, being HCV is a RNA virus, it cannot integrate into the host genome but its viral proteins such as structural (core, E1, E2) and non structural proteins (P7, NS2, NS3, NS4A, NS4B, NS5A & NS5B) can cause change in the signaling pathways and gene expression which leads to epigenetic modification of tumour suppressor genes which cause expression of oncogenes in early tumourigenesis and mutation in these oncogenes supports tumour survival and growth and cause HCC. [28]

Alcohol

Another causative factor of chronic liver disease and Hepatocellular carcinoma is alcohol consumption, which cause HCC via direct (genotoxic) and indirect mechanisms (cirrhosis). [29] In hepatocytes, primarily ethanol is metabolized into acetaldehyde by alcohol dehydrogenase in the cytosol, cytochrome P450 in microsomes and catalase in peroxisomes.

In moderate alcohol intake, Acetaldehyde is rapidly metabolized into acetate by acetaldehyde dehydrogenase in mitochondria. This acetate is rapidly released from the liver into circulation and is then metabolized into CO_2 via the Krebs cycle in heart, skeletal muscle and brain. In chronic alcohol abuse, acetaldehyde production is increased which is a highly reactive compound and toxic to hepatocytes because it forms a variety of proteins and DNA adducts that promotes glutathione depletion, lipid peroxidation and mitochondrial damage. These lead to hepatic injury, cirrhosis and Hepatocellular carcinoma. [30-32]

Aflatoxin

Aflatoxin is a mycotoxin produced by the common Aspergillus flavus and Aspergillus parasiticus. This mycotoxin is found in foodstuffs, including corn, rice, oilseeds, dried fruits and peanuts that have been stored improperly in hot, humid and unsanitary conditions. [33] When animals consume aflatoxin contaminated feed, a metabolite, aflatoxin M_1, is excreted in the milk. [34]

Aflatoxins are a group of secondary metabolites. There are four major aflatoxins known as B_1, B_2, G_1 and G_2. Among them, aflatoxin B_1 (AFB1) is the most toxic mycotoxin and the most potent naturally occuring chemical liver carcinogen and mutagen.

In the liver cells, AFB1 is metabolized into the reactive oxygen species such as aflatoxin-8,9-epoxide, which binds to the liver cell DNA and form DNA adducts namely 8,9-dihydro-8(N_7guanyl)-9-hydroxy-AFB_1(AFB_1N7-Gua). If this is not repaired before DNA replication, the DNA adducts interact with the guanine base of the DNA and cause mutational effects in the p53 tumour suppressor gene resulting in hepatocarcinogenesis. [33-36]

Other causes

Non Alcoholic Fatty Liver Disease (NAFLD) and Non Alcoholic Steatohepatitis (NASH) are the most common etiology of chronic liver disease. NAFLD is directly associated with metabolic syndrome, [37] because, the components of metabolic syndrome are the risk factors for the development of NAFLD. [38] Metabolic syndrome (MetS) is a constellation of problems which including 6 major components, they are abdominal obesity, Atherogenic dyslipidemia, Raised blood pressure, Insulin resistance ± glucose intolerance, Proinflammatory state and Prothrombotic state. [39] Obesity is the major component in metabolic syndrome, Diabetes mellitus and hyperlipedemia. Obesity is characterized by a low grade

inflammatory response. In it, there is expansion of adipose tissue leads to release of pro-inflammatory cytokines like TNFα (Tumor necrosis factor α) which is potent activator of pro-oncogenic pathways and IL-6 (Interleukin -6) which exerts cell proliferative and anti-apoptotic effects. Adipose tissue expansion decreases the release of adipose derived hormones or adipokines like adiponectin which exerts potent anti-inflammatory effects and increase the release of Leptin which exerts pro-inflammatory and pro-fibrogenic effect by activating kupffer cells and stellate cells which lead to disease progression.[40] These events are catalytic to hepatic fibrosis, cirrhosis and eventually Hepatocellular carcinoma.[41,42]

Iron over load – Iron is essential for many vital functions. But it should be regulated within limits. When the body iron exceeds which leads to iron overload and iron toxicity. Iron overload, generally defined as an increase in total body iron exceeding 5 gram. [43] Causes of iron overload may be genetic like hereditary haemochromatosis, Thalassemia syndromes, sideroblastic anaemias or acquired like alcohol abuse, dietary iron over load, exposure to heavy metals, chronic hepatitis C, NAFLD, and NASH. [44,45] Liver is the major storage place of Iron. Iron overload induces reactive oxygen species (ROS) production via Haberweiss reaction (Interaction between iron and superoxide) and Fenton reaction (Interaction between iron and hydrogen peroxide). These ROS damages the biomolecules and promotes oncogenes activation, DNA strand breaks, lipid peroxidation, mutagenesis which leads to liver injury, fibrosis, cirrhosis and eventually Hepatocellular carcinoma. [46]

CLINICAL MANIFESTATIONS OF HCC

At early stage, patients with HCC are asymptomatic. The common signs and symptoms are right upper quadrant pain, palpable mass in right upper quadrant due to enlarged, irregular and nodular liver, loss of appetite, loss of weight, fatigue, fever, jaundice, Ascites, spleenomegaly, muscle wasting and abnormal liver function test.

During the terminal stage, the patient may present with Ascites, variceal bleeding, peripheral odema, hepatic encephalopathy, cachexia, dyspnoea, anorexia, vomiting and psychiatric distress.

Para neoplastic manifestations are hypercholesterolemia, erythrocytosis, hypoglycaemia, hyper calcaemia, thrombocytosis, arterial hypertension, dermatomyositis and peripheral polyneuropathy.[47,48]

Staging of HCC

Staging of cancer is very important for patient management and research advancement. Several staging systems are there. But American Joint Committee on Cancer (AJCC) / Union Internationale Contre le Cancer (UICC) staging system is most useful. Because, it is based on the standard system of tumor, node and metastasis classification and its capacity to help more accurately predict the prognosis and to direct post operative adjuvant therapy and they have been updated regularly since the first edition in 1977. [49,50]

Diagnosis

Because of its silent nature, diagnosis of HCC in early stage is very difficult. 80% of the cases will be diagnosed during advanced stage. The diagnostic techniques for HCC include serum markers, various imaging modalities and histological analysis. [51]

Serum markers – Number of serum markers are there to diagnose HCC. They are Alpha Feto protein (AFP), Lens culinaries agglutinin-reactive AFP (AFP-L_3), Des-gamma carboxy prothrombin (DCP), α-L-Fucosidase, Glypican-3, Squamous cell carcinoma antigen (SCCA), Golgi protein 73, Hepatocyte growth factor (HGF), Transforming growth factor β_1 (TGF-β_1), vascular endothelial growth factor (VEGF), Serum proteomics.

Alpha Feto Protein (AFP) – AFP is a fetal specific glycoprotein, which is elevated in hepatocarcinogenesis, embryonic carcinoma, gastric cancer, lung cancer and disease associated with high degree of hepatocyte regeneration in absence of cancer. AFP value above 400-500ng/ml has been considered to be diagnostic for HCC. [51]

Lens culinaris agglutinin-reactive AFP – it is otherwise known as AFP-L_3 which is Isoform of AFP. AFP-L_3 percentage of total AFP concentration [(AFP-L_3 / total AFP) X 100] or AFP-L_3 % has been used as a marker for early diagnosis for assessment of therapeutic effects and predicting the prognosis of HCC. [52] AFP-L_3 is produced by malignant liver cells. AFP-L_3 can be detected in the serum of approximately 35% of the patients with small HCC (<2cm). The AFP-L_3 positive HCC has potential for rapid growth and early metastasis. [53,54]

Des-gamma carboxyprothrombin (DCP) – DCP is an abnormal prothrombin without carboxylation of the 10 glutamic acid residues in the N-terminus and is devoid of coagulation activity. It is also known as PIVKA-II (protein induced by vitamin K2 absence/ antagonist-II). It completely lost the normal prothrombin function and may play an important role in the malignant proliferation of HCC. Therefore, DCP is specific to HCC and less prone to elevation during chronic liver diseases. So DCP is a potential serum marker of early diagnosis of HCC and marker of intrahepatic metastasis. [55-57]

α-L-Fucosidase - It is lysosomal enzyme present in mammalian tissues where it degrade fucose containing fucoglyco-conjugates. Activity of this enzyme is detectable in healthy subjects. But this enzyme level is increased in HCC.[58]

Glypican3- It is cell surface glycoprotein. This protein is not detectable in normal tissues except placenta and fetal liver. But they are expressed and significantly increased in HCC patients sera.[59]

Squamous cell carcinoma antigen - It is a serine protease inhibitor, which is physiologically expressed in the skin and other Squamous epithelial cells. This level will be increased in head and neck cancers and other epithelial cancers. This antigen levels have been increased in HCC also.[60]

Golgi Protein 73 (GP 73) - It is a resident Golgi-specific membrane protein expressed by biliary epithelial cells in normal liver. This levels are elevated in HCC patients.[61]

Hepatocyte Growth Factor (HGF) - It is produced in various body organs and it is a potent hepatocyte mitogen and may stimulate the proliferation and invasiveness of

human HCC cells via c-met receptors. Serum HGF levels are significantly elevated in HCC patients. Patients with serum HGF concentration greater than 0.6 ng/ml had HCC. HGF levels greater than or equal to 1.0 ng/ml have been associated with poor survival in HCC. So it can be used as a prognostic marker in HCC. [62]

Transforming growth factor-beta 1(TGF-β1) - It is a multifunctional factor. It plays a vital role in the regulation of growth and differentiation of normal and transformed cells, angiogenesis, extra cellular matrix formation, immunosuppression and carcinogenesis. This level will be significantly high in HCC patients. [63]

Vascular Endothelial Growth factor (VEGF) - It is an endothelial cell Mitogen that initiates and promotes neovascularization and endothelial cell proliferation. It plays a vital role in regulating angiogenesis. This level will be significantly high in HCC patients.[64]

Imaging Techniques for HCC - A number of imaging modalities are available for the detection of HCC. They are Ultrasound (US), Computed tomography (CT), Magnetic Resonance imaging (MRI), and Positron Emission Tomography (PET). They are all non invasive techniques, which help for detection of HCC lesions, evaluation of focal liver lesions and staging of HCC. [65] When diagnosis is not achieved by these non invasive techniques, other invasive techniques are used such as Iodized oil-CT, CT during hepatic arteriography (CTHA), CT arterial Portography (CTAP), Conventional hepatic angiography and Cytological examination of a suspected lesion by US guided fine needle aspiration biopsy. [51]

Histopathological examination - Finally, histopathological examination of liver biopsy or suspected lesion is considered the ideal method to confirm the diagnosis of HCC and staging of HCC. It is mandatory to decide the treatment modalities.[51]

MANAGEMENT

Resection is the first line of therapy for localized HCC without cirrhosis. But it is not suitable for cirrhotic patients and patients with portal vein hypertension. In these situations Liver transplantation is the best therapy. But it can only be performed in patients in early stage of HCC. Percutaneous ablation such as Percutaneous ethanol Injection (PEI) and Radiofrequency ablation (RFA) is other treatment options for the patients who are not suitable for resection and Liver transplantation. Other palliative treatment modality for HCC is Chemoembolization.

Being HCC is most chemo-resistant tumor, systemic chemotherapy with cytotoxic agents such as doxorubicin, Cisplatin, 5-fluorouracil, interferon and hormonotherapy show marginal or poor improvement. [66]

Surgical procedures are effective in early stage of HCC. But 80% of the HCC are diagnosed in the advanced stage. The palliative therapies such as radiotherapy and chemotherapy are shown more side effects. Because of these disadvantages, patients seek alternative therapies to improve the quality of life or survival period such as herbal medicines. Because of the presence of bioactive phytocompounds, the herbs show good anticancer activities without that much side effects. To confirm this statement, it requires advanced level research on herbal medicine.

CONCLUSION

Despite significant advances in medicine, Hepatocellular carcinoma remains a major cause of death in the world. Early diagnosis and continued improvement in surgical and nonsurgical procedures may increase survival rate. Above all, 'Prevention is better than cure'. So, preventive measures such as vaccinations, universal screening of blood products, use of safe injection practices, treatment and education to alcoholics and intravenous drug users, antiviral therapy and changing the food habits may reduce the death rate as well as occurrence of HCC.

REFERENCES

1. Lisa P Waller, Vrushak Deshpand, Nikolaos Pyrsopoulos. Hepatocellular carcinoma: A comprehensive review. World Journal of Hepatology. 2015; 76(26): 2648-2663.
2. Jim Um Kim, Mohamed I F Shariff, Mary M E Crosseu, Maria Gomez-Romero, Elaine Holmes, I Jane Cox, Haddy K S Fye, Ramou Njie, Simon D taylor-Robin Son. Hepatocellular carcinoma: Review of disease and tumour biomarkers. World Journal of Hepatology. 2016; 8(10): 471-484.
3. Jelic s, Sotriopoulous G C, on behalf of the ESMO Guidelines working group. Annals of Oncology. 2010; 21(5): 59-64.
4. Sara Badvie. Hepatocellular Carcinoma. Postgrad Med J. 2000; 76: 4-11.
5. Santhosh Gaddikeri, Micheal F. Mc Neelay, Carolyn L. Wang, Puneet Bhargava, Manjiri K Dighe, Matthew M C Yeh, Theodore JayDubinsky, Orpheus Kolokythas, Neeraj Lalwani. Hepatocellular Carcinoma in the non cirrhotic liver. American journal of Roentgenology. 2014; 203: 34-47.
6. Jessica Goldman, Marc Solomon, Sohail Contractor. Hepatocellular Carcinoma – Review of treatment options with percutaneous Ablative Therapies. Clinics in Oncology. 2016; 1(1107): 1-6.
7. Luiza Vitelo Andrighetto, Aline Kirjner Poziomycle. Serum leptin levels and Hepatocellular Carcinoma: Review article. ABCD Arq Bras Cir Dig. 2016; 29(4): 276-278.
8. Liovet Jm, Bru C, Bruix J. Prognosis of Hepatocellular Carcinoma. The BCLC Staging Classification. Semin Liver Dis. 1999; 19: 329-338.
9. Ran Xu Zhu, Wai Kay Seto, Ching-Lung Lai, Man-Fung Yuen. Epidemiology of Hepatocellular carcinoma in the Asia-pacific region. Gut and liver. 2016; 10(3): 332-339.
10. Marcos Antonio Gomes, Denise Goncalves Priolli, Jose Guilherme Tralhao, Maria Filomena Betelho. Hepatocellular Carcinoma: Epidemiology, biology, diagnosis and therapies. Rev.Assoc.Med.Bras. 2013; 59(5): 514-524.
11. Renumathy Dhanasekaran, Alpha Limaye, Riniel Cabrera. Hepatocellular Carcinoma: Current trends in world wide epidemiology, risk factors, diagnosis, and therapeutics. Dove press journal: Hepatic Medicine: Evidence and research. 2012;4:19-37.
12. Katherine A. Mc Glynn, Thomg London W. The global Epidemiology of the Hepatocellular Carcinoma, Present and future. Clin Liver Dis. 2011; 15(2): 1-22.
13. Sene Waly Raphael, Zhang Yangde, Chen Yu Xiang. Hepatocellular Carcinoma: Focus on Different Aspects of Management. ISRN Oncology. 2012; 1-12
14. Arun J Sanyal, Seung Kew Yoon, Reccardo Lencioni. The Etiology of Hepatocellular Carcinoma and Onsequences for Treatment. The oncologist. 2010; 15(4): 14-22.
15. Gadikkeri et al. Hepatocellular Carcinoma in the Non cirrhotic Liver. American Journal of Roentgenology. 2014; 203: 34-47.
16. Johannes Wiegand, Thomas Berg. The Etiology, Diagnosis and prevention of Liver cirrhosis. Dtsch Arztebl Int. 2013; 110(6): 85-91.
17. Nabil bdel-Hamed. Update to risk factors for Hepatocellular carcinoma. Int.J. Med.Med.Sci. 2009; 1(3): 038-043.
18. Jeans-Charles Nault. Pathogenesis of Hepatocellular carcinoma according to aetiology. Best Practice & Research Clinical Gasteroenterology. 2014; 28: 937-947.

19. Birke Bartosch. Heaptitis B and C viruses and Hepatocellular carcinoma. Viruses. 2010; 2: 1504-1509
20. Chemin I, Zoulim F. hepatitis B virus induced Hepatocellular carcinoma. Cancer letters. 2009; 286: 52-59.
21. Adrian M Di Bisceglie. Hepatitis B and Hepatocellular carcinoma. Hepatology. 2009; 49(5): S56-S60.
22. Patrick Arbuthnot, Michael kew. Hepatitis B virus and Hepatocellular cellular carcinoma. Int J Exp Pathol. 2001; 82(2): 77-100.
23. Ngeryan V T T, Law M G, Dore G J. Hepatitis B related Hepatocellular carcinoma. Epidemiological characteristics and Disease Burden. J Viral Hepat. 2009; 16(7): 453-463.
24. Luis Jesuino de oliveria Andtrade, Argemiro D'Oliveira, Junior, Rosangela carvalho melo, Emmanuuel conrado De Souza, Carolene Alves Costa Silva, raymundo Parana. Association between Hepatitis C and Hepatocellular Carcinoma. J Glob Infect Dis. 2009; 1(1): 33-37.
25. Ana Tereza R.Viso. Pathogenesis of hepatitis C- HCV consensus 2007. BJID. 2007; 11(1): 14-19.
26. Stephen L. Chen, Tomothy R Morgan. The Natural History of Hepatitis C virus (HCV) Infection. Int J Med Sci. 2006; 3(2): 47-52.
27. Yujin Hoshida, Bryan C.Fuchs, Nabeel Bardeesy, Thomas F.Baumert, Raymond T.Chung. Pathogenesis and Prevention of hepatitis C virus-Induced Hepatocellular carcinoma. J Hepatol. 2014; 61(10): S79-S90.
28. Miriam Canavese, Danushka Wijesun dara, Guy J Mddern, Brande Grubor-Bauk, Ehud Hauban. Hepatitis C virus drives the pathogenesis of Hepatocellular carcinoma: from immune evasion to carcinogenesis. Clinical & Translational Immunology. 2016; 5(101): 1-6.
29. Gianni Testino, Silvia Leone, Paolo Borro. Alcohol and Hepatocellular carcinoma: A review and a point of view. World Journal of Gastroenterology. 2014; 20(43): 15943-15954.
30. Bin Gao, Raman Bataller. Alcoholic Liver Disease: Pathogenesis and New Therapeutic Targets. Gastroenterology. 2011; 141(5): 1574-1585.
31. Eric S Orman, Gemma Odena, Ramon Bataller. Alcoholic liver disease: Pathogenesis, management and Novel targets for therapy. J Gastroenteol Hepatol. 2013; 28(01): 77-84.
32. Sreetha Sidharthan, Shyam Kottilil. Mechanism of alcohol induced Hepatocellular carcinoma. Hepatol Int. 2014; 8(2): 452-457.
33. Adbu Selim Hamid, Isaias Gottom Tesfamariam, Yucheng Zhang, Zhen Gui Zhang. Aflatoxin B1-induced Hepatocellular carcinoma in developing countries: geographical distribution, mechanism of action and prevention (Review). Oncology letters. 2013; 5: 1087-1092.
34. Yan Liu, Felicia Wu. Global Buren of Aflatoxin-Induced Hepatocellular Carcinoma: A Risk assessment. Environ Health Perspect. 2010; 118(6): 818-824.
35. Kew MC. Aflatoxin as a cause of Hepatocellular carcinoma. J Gastrointestin liver Dis. 2013; 22(3): 305-310.
36. Jiejun Shi, Jiangtu He, Jing Lin, Xin Sun, Fenyong Sun, Chao Ou, Cizhong Jiang. Distinct response of the hepatic transcriptome to Aflatoxin B_1 induced Hepatocellular carcinogenesis and resistance in rats. Scientific Reports 6. 2016; article number: 31898
37. Sass DA, Chang P, Chopra K B. Non alcoholic fatty liver disease: a clinical review. Dig Dis Sci. 2005; 50: 171-180.
38. Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connections. Hepatology. 2010; 51(5): 1820-1832.
39. Scott M. Grundy, Bryan Brewer H, James I Cleeman, Sidney C. Smith, Claude Lenfant. Definition of Metabolic syndrome. Circulation. 2004; 109: 433-438.
40. Richard N Redinger. The Pathophysiology of Obesity and its Clinical Manifestations. Gastroenterology & Hepatology. 2007; 3(11): 856-863.
41. Adviti Naik, rok Kosir, Damjana Rozman. Genomic aspects of NAFLD Pathogenesis. Genomics. 2013; 102: 84-95.
42. Fancosis Cauchy, Jacques Belghiti. A clinical perspective of the link between metabolic syndrome and Hepatocellular carcinoma. Journal of Hepatocellular Carcinoma. 2015; 2: 19-27.
43. Micheal C Kew. Hepatic Iron Over load and Hepatocellular Carcinoma. Liver cancer. 2014; 3: 31-40.
44. Juxing Chen, Maja Chloupkova. Abnormal iron uptake and liver cancer. Cancer Biology & Therapy. 2009; 8(18): 1699-1708.
45. Antonello Pietrangelo. Iron in NASH, chronic liver disease and HCC: How much iron is too much?. Journal of Hepatology. 2009; 50: 249-251.
46. Sayed Hossein Davoodi, Yasaman Jamshidi-Naeini, Saeideh Esmaeili, Sara Sohrabvandi, Amir M Mortazavian. The Dual Nature of Iron in Relation to Cancer: A Review. Iran J Cancer Prev. 2016; 9(6):e5494.
47. Virginia Chih-Yi Sun, Linda Sarna. Symptom management in Hepatocellular Carcinoma. Clin J Oncol Nurs. 2008; 12(5): 759-766.
48. Ali A Mokdad, Amit G Singal, Adam C Yopp. Liver Cancer. JAMA. 2015; 314(24): 2701.
49. Hollins P Clark, Forrest Carson W, Peter V Kavanagh, Coty P H Ho, Perry Shen, Ronald J Zagoria. Staging and Current treatment of Hepatocellular Carcinoma. RadioGraphics. 2005; 25(1) S3-S23.
50. Somasundaram Subramaniyam, Rabin K. Kelly, Alan P Venook. A review of Hepatocellular carcinoma staging sytems. Chin Clin Oncol. 2013; 2(4):33.
51. Asmaa I Gomaa, Shahid A khan, Edward LS Leen, Iman Waked, Simen D Taylor-Robinson. Diagnosis of Hepatocellular carcinoma. World J Gastroenterol. 2009; 15(11): 1301-1314.
52. Leerapun et al. the Utility of AFP-L_3 % in the Diagnosis of Hepatocellular Carcinoma: Evaluation in A U.S. Referral Population. Clin gastroenterol Hepatol. 2007; 5(3): 394.
53. Dave Li, Tonya Malloy, Shinji Satomura. AFP-L3: a new generation of tumor marker for Hepatocellular Carcinoma. 2001; 313(1-2): 15-19.
54. Jiwen Cheng, Wanli Wang, Yingjun Zhang, Xi Lu, Muxing Li, Zheng Wu, Zhengwen Liu, Yi LU, Bo Wang. Prognostic Role of Pre-Treatment Serum AFP-L3% in Hepatocellular carcinoma: Systematic Review and Meta Analysis. PLoS ONE. 2014; 9(1): e87011.
55. Hie-Won Hann, Dave Li, Hiroyuki Yamada, Shinji Satomura, Robert Coben Anthony J Dimarina. Usefulness of Highly sensitive AFP-L3 and DCP in Surveillance for Hepatocellular Carcinoma in Patients with Normal Alpha-Fetoprotein. J med Microb Diagn. 2014; 3(1): 6 pages.
56. Yu-Sheng Zhang, Jia-Hui Chi, Shu-Xiang Cui, Zhi-Yu-Song, Xian-Jun Qu. Des-γ-Carboxy Prothrombin (DCP) as a Potential Autologous Growth Factor for the Development of Hepatocellular carcinoma. Cell Physiol Biochem. 2014; 34: 903-915.
57. Rong Zhu et al. Diagnostic Performance of Des-γ-Carboxy Prothrombin for Hepatocellular Carcinoma: A Meta-Analysis. Gastroenterology Research and Practice. 2014. Article ID 529314. 9 pages.
58. Fawzy Montaser M, Amin Sakr M, Omar Khalifam. Alpha-L-Fucosidase as a tumour marker of Hepatocellular carcinoma. Arab J Gastroenterol. 2012; 13(1): 9-13.
59. Hussein F Zahran, Mohey EI- Deen I, Sayed M Sabea, Zahran F Ibrahim. Glypican-3 as a tumor marker in Hepatocellular carcinoma. BCAIJ. 2013; 7(2): 71-77.
60. Nabil El- Kady, et al. Squamous Cell Carcinoma Antigen as a Tumour Marker in Patients with Hepatocellular Carcinoma. Med. J. Cairo Univ. 2009; 77(1): 379-383.
61. Yang et al, Golgi protein 73 as a biomarkers for Hepatocellular carcinoma: A diagnostic meta-analysis. Experimental and Therapeutic Medicine. 2015; 9 1413-1420.
62. Yamagami et al. serum Concentration of Human Hepatocyte Growth Factor Is a Useful Indicator for Predicting the occurrence of Hepatocellular Carcinomas in C-Viral Chronic Liver Diseases. CANCER. 2002; 95(4): 824-834.
63. Song et al. transforming Growth Factor- β1 as a useful Serologic Marker of Small Hepatocellular Carcinoma. CANCER. 2002; 94(1): 175-180.
64. Sharma B K, Srinivasan R, Chawla Y K, Chakraborti A. Vascular endothelial growth factor: Evidence for autocrine signaling in Hepatocellular carcinoma cell lines affecting invasion. Indian Journal of Cancer. 2016; 53(4): 542-547.
65. Chou R, Cuevas C, Fu R, Devine B, Wasson N, Ginburg A, Zakher B, Pappas M, Graham E, Sullivan SD. Imaging Techniques for the Diagnosis of Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. Ann Intern Med. 2015; 162(10):697-711.
66. Ingle et al. Development and novel therapeutics in Hepatocellular carcinoma: a review. Therapeutics and Clinical Risk Management. 2016;12:445-455.