ejpmr, 2016,3(10), 116-123.

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 3294-3211

EJPMR

HEPATIC CARCINOMA: A GLOBAL MENACE

Ashif Iqubal[1], Kashif Iqubal[2] and Syed Ehtaishamul Haque[1]*

[1]Department of Pharmacology, Faculty of Pharmacy, Jamia Hamdard, New Delhi, India – 110062.
[2]Department of Pharmacy, Kalka Institute for Research and Advanced Studies, Partapur by-pass, Meerut, U.P, India.

***Correspondence for Author: Dr. Syed Ehtaishamul Haque**

Department of Pharmacology, Faculty of Pharmacy, Jamia Hamdard, New Delhi, India – 110062.

Article Received on 27/07/2016 **Article Revised on 17/08/2016** **Article Accepted on 07/09/2016**

ABSTRACT

Hepatic carcinoma is emerging as a global challenge and is the leading cause of mortality worldwide. Fatty liver disease, hepatitis, alcoholic liver disease (ALH), non-alcoholic fatty liver disease (NAFLD), liver cirrhosis and associated metabolic syndromes are some common causes of hepatic sarcoma. Pathogenesis of hepatic sarcoma is multifactorial in origin and problem lies in delayed diagnosis as most of the cases are diagnosed at an advanced stage which is hard to treat. Currently available treatment regimen comprises of curative resection, liver transplant, embolization, ablation and chemotherapy. Among the different treatment options available liver transplant emerges as the most acceptable regimen with maximum acceptance. However, chemotherapy (cisplatin, flurouracil or irinotecan) in combination with sorafenib emerges as another curative regimen. Now-a-days targeted molecular therapy is being used in order to minimize the side effect and increase the success rate. This article provides an overview of epidemiology, pathogenesis and diagnostic approach for hepatic sarcoma and also deals with the overall treatment options available.

KEYWORDS: Hepatic sarcoma, hepatitis, cirrhosis, embolization, ablation, transplant, sorafenib, β catenin, Myc protein.

INTRODUCTION

Hepatic carcinoma (HCC) is most of the time referred as malignant hepatoma[1] and is the 3rd most common cause of death from cancer and 5th most common form of cancer.[2] HCC often occurs in the background of a cirrhotic liver. According to WHO record more than 500,000 deaths have been recorded with hepatic carcinoma.[3] Asia and sub-Sahara Africa region are most prone to the pathogenesis of hepatic carcinoma.[4] Prognosis of HCC involves multiple processes and it begins with genetic alteration in hepatocytes.[5] Chronic hepatitis C virus infection (HCV), alcohol intake and non-alcohol fatty liver disease (NAFLD) are the some common causes of HCC.[6] Hence, there is an urgent need to look up for the therapy of hepatic cancer as it is growing day by day. Beside clinical studies, preclinical studies using animal models are helpful as physiology and genetic makeup of human and rodents are very much similar.[7]

Epidemiology

If we talk about the epidemiology of hepatic carcinoma, we will find that the USA, Asia and sub Sahara-Africa region is most prone to HCC.[4] in USA it is one of the fastest growing causes of mortality.[8] Since past two decades, the occurrence of HCC increased from 2.6/1000 to 5.2/1000 and if we talk about the occurrence of HCC in America, it has increased from 4.6% to 13.1% among males.[9] Globally average age at which HCC is diagnosed is above 65 years and probably is the reason for a higher range of mortality world-wide.[10]

Pathophysiology

The occurrence of hepatic carcinoma is multifactorial in origin. Beasly first time linked the cause of hepatic carcinoma (HCC) with Hepatitis B in 1981[11] but later it was seen that apart from hepatitis B, liver cirrhosis is also one of the underlying causes of hepatic carcinoma[12], infact negative markers of Hepatitis B and C infection are other causes of HCC.[13] in recent year lot of work has been done to elucidate the genetic pathway for HCC and p53, PIKCA and β-catenin genes were found to be most common mutant genes in HCC individual.[14] There are many documented evidence showing the role of dysplastic regenerative nodules in the pathogenesis of hepatic carcinoma. Some researcher suggested that infection of Hepatitis B & C attenuate the HCC by initiating the body's own immune system to attack hepatic cell and this constant damage of hepatic cell followed by repair though genetic encoding pathway often lead to mistake during repair leading to hepatic carcinoma.[15] Apart from these causative agents, consumption of large amount of alcohol, Aflatoxin from aspergillus, imbalance dietary intake, NAFLD/NASH and metabolic syndrome are some other pathogenic

causes of hepatic cancer.[16,17] Brief outline of pathogenesis of HCC is shown in figure 1.

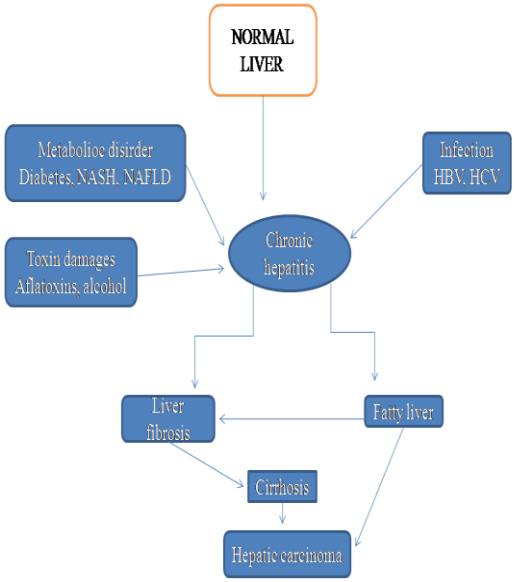

Figure 1. Pathophysiology of hepatocellular carcinoma[18]

TYPES OF HEPATIC TUMOR[14]

Benign Liver Tumors

These are actually not tumors and can be successfully removed by surgery. There is no chance to develop into cancerous state.[14]

Hemangioma

A common type of liver cancer that is related with malfunctioning of blood vessels. It usually begins from blood vessels and there is no symptomatically attention needed and most often need no treatment but in some cases, surgery is performed to remove this type of cancer.[14]

Hepatic adenoma

Hepatic adenoma is benign in nature which originates from hepatocytes and sometime causes symptomatic attention as mass is seen in the stomach causing abdominal pain and recurrent fever (low grade). There is always a probability that this type of cancer may burst and cause heavy loss of blood and could be fatal. Birth pills in female and anabolic steroids' in male are common causes of hepatic adenoma.[14]

Focal nodular hyperplasia (FNH)

These are tumors-like outgrowth from multiple cells like, cells of bile duct, liver and connective tissue. Infact FNH is benign in nature but it is always advised to remove this outgrowth by surgery.[14]

Hepatocellular carcinoma

This is the most common type of primary hepatic cancer that originates from hepatocytes and at the later stage spread to other body parts. They have different pattern of growth (1) a single tumor that grow larger initially, spread to other parts of the body later (2) small cancerous nodules that spread out throughout the hepatic cells and is linked with people suffering from cirrhosis.[14]

Intrahepatic/ extra hepatic cholangiocarcinoma (Bile duct cancer)

These types of cancer constitute 10--20% of liver cancer. Depending upon the origin, tumors may be classified. If tumor originates from the section of duct inside the liver, it is called as Intrahepatic cholangiocarcinoma and if from the section of duct outside the liver, it is called extra hepatic cholangiocarcinoma. Bile duct cancer is a bit difficult to treat.[14]

Angiosarcoma

This type of cancer is rare and in UK only 10 cases of angiosarcoma are diagnosed. Angiosarcoma is often called as haemangiosarcoma and involves hepatic blood vessels of sinusoids. Vinyl chloride, thorium dioxide, arsenic and radium are some of the causative chemical agents for angiosarcoma. Angiosarcoma is mainly diagnosed at later stage of life (after age of 65).[14]

Hepatoblastoma

Hepatoblastoma is another rare hepatic cancer that occurs in children at the age less than 4 years. In UK 20 cases of hepatoblastoma is diagnosed every year. Doctors mainly combine surgery with chemotherapy there and the success rate is 66.66%.[14]

Metastatic Liver cancer

It has been seen that most of the time cancer is diagnosed in the liver but it did not originate from it, rather have been spread from other organs to liver like pancreas, colon, stomach, breast and lungs. As these type of cancers have spread out from its original place of origin to liver, hence termed as secondary hepatic sarcoma.[14]

Risk factors

There are several risk factors for hepatic carcinoma as discussed below and shown in the following figures.

Gender: Hepatic carcinoma is often associated with male as compared with female.[19]

Race

People from United States of America, Asia, Pacific Island and Sub-Sahara Africa are mostly susceptible to hepatic carcinoma.[10]

Hepatitis B and C

It is one of the most common causes of hepatic cancer worldwide. Hepatitis B and C often leads to liver cirrhosis which ultimately progresses into hepatic cancer as shown in figure 2. Hepatitis C is more common cause of HCC in Asian population where as Hepatitis B is more common to American population.[20]

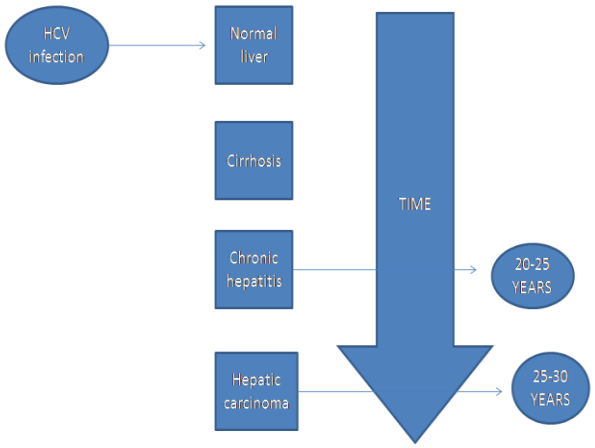

Figure 2. Progression of hepatocellular carcinoma from hepatitis C infection (HCV) [21]

Cirrhosis

There is always an increased risk of hepatic carcinoma among cirrhotic individual and regular medication and routine check-up is advised to such individuals (figure 3).[22]

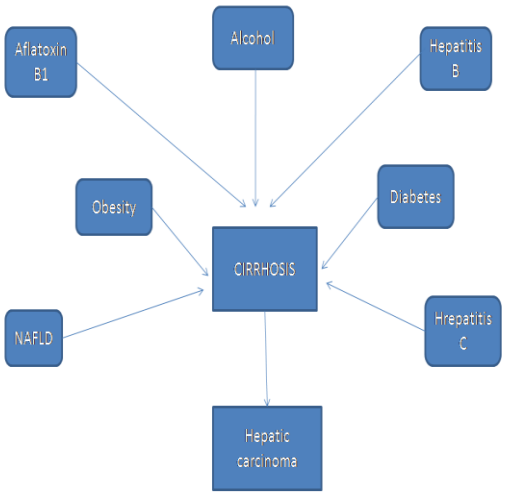

Figure 3. Cirrhosis and hepatic carcinoma[23]

Nonalcoholic fatty liver disease (NAFLD)

Recently it has been established that NAFLD causes hepatic cancer if remain untreated as shown in figure 4 & is directly associated with the metabolic syndrome.[24] Normally in NAFLD, biochemical markers are elevated[24], indicating as liver is not functioning properly.[24]

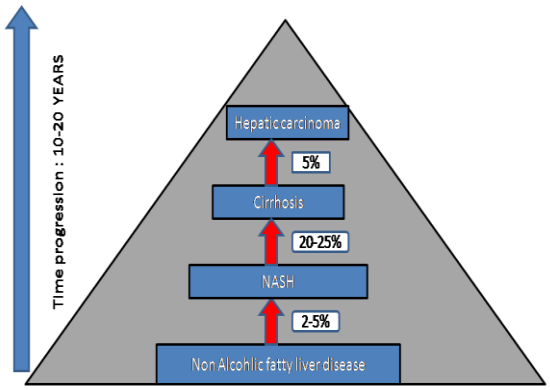

Figure 4. NAFLD and hepatic carcinoma [25]

Primary biliary cirrhosis (PBC)

Sometime autoimmune disease leads to cirrhosis. In PBC, hepatic cells get damaged and destroyed due to autoimmune state leading to cirrhosis and ultimately hepatic carcinoma.[26]

Alcohol

Consumption of alcohol often lead to diseased state termed as alcoholic fatty liver disease in which normal liver is transformed into fatty liver and hepatocyte begins to degenerate and biological markers of liver elevate and gradually fatty liver is transformed into cirrhotic liver and than if remain untreated leads to hepatic carcinoma as shown in figure 5.[27]

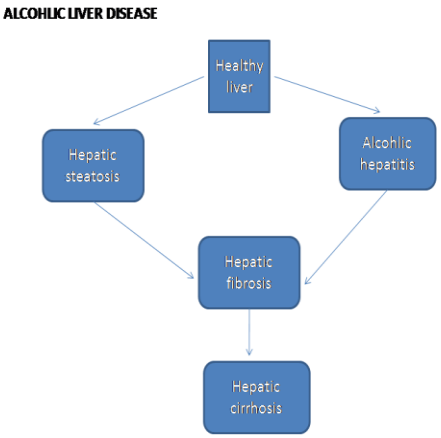

Figure 5. Prognosis of hepatocellular carcinoma from alcoholic intake [28]

Metabolic syndrome

Metabolic syndrome like diabetes (insulin resistance)[29], hypertension, dyslipidemia, hypothyroidism and

obesity[30] leads to hepatic carcinoma (HCC) as shown in figure 6.[31]

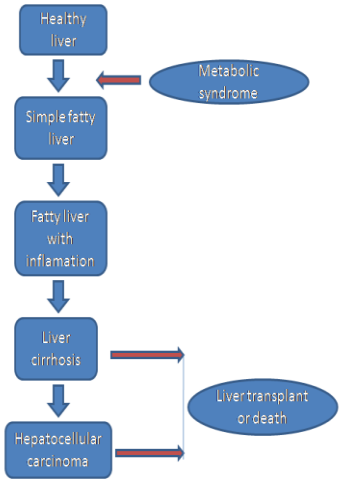

Figure 6. Effect of metabolic syndrome and progression of hepatic carcinoma[32]

Aflatoxin

Aspergillus is a known fungus in pathogenic world which is found in peanuts, soybean, wheat, ground nuts, corn etc. and contains a toxin known as aflatoxins which causes hepatitis.[33]

Diseased condition

Tyrosinemia α 1 antitrypsin deficiency[34], porphyria cutanea tarda[35], glycogen storage disease and Wilson disease[36] often leads to hepatic carcinoma.[34]

Anabolic steroids

Anabolic steroids are most commonly used by sports person and athletes and adult who joins gym and such class of people regularly takes anabolic steroid to gain mass and energy which leads to hepatic cancer on long term use.[37]

Chemicals

Vinyl alcohol[38], thorium dioxide and arsenic are some of the most common carcinogenic agents. Vinyl alcohol and thorium dioxide (Thorotrast)[39] were used in early time as injectables before X-ray and later on it was realized that these chemicals cause mutation and leads to hepatic cancer. Arsenic present in water at more than threshold level leads to hepatic cancer in rural areas of developing countries.[40]

DIAGNOSIS

It has been seen that hepatic carcinoma is often diagnosed at an advanced stage. Early detection of hepatic cancer however, is accidental mainly found during routine check-up of high-risk patients (cirrhotic, hepatitis B & C, α1 antitrypsin deficient individuals and patients suspected of NAFLD). Some common diagnostic parameter used by clinician for diagnosis of hepatic carcinoma are as follow**:**

Blood test (Anemia)

Abnormal complete blood count (CBC) is the primarily indicator of cancer which needs to be further taken into consideration.[41]

Thrombocytopenia

Platelets count less than 100,000/µL indicates the onset of cancer, however, other clinical parameters must be taken into consideration to ascertain the disease.[41]

Hyponatremia

Liver cirrhosis and sadistic patient are prone to develop hyponatremia.[41]

Serum creatinine

Increased serum creatinine level with respect to elevated liver enzyme signifies the onset of hepatic oncogenesis.[41]

Alpha fetoprotein (AFP)

It is an AFP gene encoded protein found in humans. Serum level of α-fetoprotein gives an idea of the status of hepatic carcinoma[42] as shown in Table 1.

Table 1. Serum alpha-fetoprotein (AFP) determination in liver disease[42]

Alpha-fetoprotein (nag/ml)	Interpretation
> 400-500	HCC likely, if accompanied by space-occupying solid lesion (s) in cirrhotic liver or levels are rapidly increasing. Diffusely growing HCC, may be difficult to detect on imaging. Occasionally in patients with active liver disease (particularly HBV or HCV infection) reflecting inflammation, regeneration or seroconversion.
<400	Frequent regeneration/inflammation (usually in patients with elevated transaminases and HCV). Regeneration after partial hepatectomy. If a space-occupying lesion and transaminases are normal, suspicion for HCC.

Imaging study

Ultrasonography

It is one of the most common tools used by clinicians to diagnose the disease. Although it does not provide better anatomical status of sarcoma when considered alone but gives better idea when combined with histopathological result and helps to decide the line of treatment.[43]

CT scan

Constitute the arterial phase, portal phase and washout phase hence some time called as triple phase CT scan. CT scan is regarded as one of the most accurate diagnostic tools that define the shape, size and location of the tumor. even hypo vascular pattern can be seen with CT scan. This tool also diagnoses the visualization of tumor capsule and portal vein invasion.[43]

MRI (Magnetic Resonance Imaging)

It is often a preferred method over CT scan as it is radiation free and has a sensitivity of 81% and specificity of more than 84%. MRI clarify the shape, size and location of the tumor within the liver and also determine the amount of intra tumoral fat and glycogen present.[43]

Biopsy

An invasive method in which hepatic cells are removed with the help of a needle and histopathological study is performed by the expert. It is a painful procedure often associated with the increased risk of infection.[44]

TREATMENT

It is one of the most challenging tasks to decide the line of treatment of hepatic carcinoma. Decision is solely based on the grade/ stage of carcinoma and overall condition of the liver. Followings are some of the normal lines of treatment.

Surgery

Procedure to remove part of tumor is called as partial hepactomy and used in a situation of single tumor localized at a particular part of the liver and has yet not been spread to another part of liver. The success of tumor removal depends upon (1) location of the tumor (2) number of tumors (3) distribution of tumors and (4) amount of liver removed.[45]

Liver transplant

If matching liver in available and patient is economically sound, liver transplantation is the best option available till date. It is mainly used when tumor can't be removed by surgery. Some time post operative complications have been seen as the immunosuppressant drugs which are prescribed for 4-5 years, suppresses the body immune system resulting into a lot of clinical complications.[46] Moreover, there is always a chance of graft rejection (up to 6-8 years).[46] In spite of all these complications success rate of liver transplant is still on the higher side.[47,48]

Embolization

Embolization is a process of curtailing the blood supply to cancerous cells by blocking the artery which supplies blood to those sarcoma cells without affecting the normal portal artery and veins. Blocking of the blood supply to cancerous cells will automatically destroy the tumor.[49]

Arteriolar embolization

It is also known as Trans Arteriolar Embolization (TAE). In this process, catheter is used through small cut on thigh and a dye is injected along with this catheter to monitor the movement of the dye through X-ray.[50]

Chemoembolization

Sometimes called as Trans Arteriolar Chemoembolization (TACE). In this method, a bed is used which act as chemotherapeutic agent.[49]

Radioembolization

This method involves the use of radioisotopes that get stuck in the hepatic artery and radioactive substance is released into tumor cells. This method is often termed as Trans Arteriolar Radioembolism (TARE).[51]

Liver tumor ablation technique

This method involves destruction of tumor by use of heat or microwave. Depending on the source of heat, different sub-methods are used such as radio frequency ablation, microwave ablation and ethanol-induced ablation.[52]

Radio frequency ablation

In this method heating probe is used which generate heat and destroy tumors. This method is limited only to small tumor size (less than 7 cm).[53]

Microwave ablation

In this method source of heat is microwave and heating probe is used directly on the tumor instead of the whole liver.[54]

Ethanol ablation

In this method ethanol is used to destroy the cancerous cells. This method is limited to cancer cell of size less than 2 - 3cm only.[55]

Systemic chemotherapy

Systemic chemotherapy mainly involves administration of hemotherapeutic drugs via intravenous route[56] but newer drugs can be given via oral routes also.[57] 5 Fluorouracil (5-FU) is one of the most common drugs used against hepatic cancer[58] and most of time it is used in combination with oxaliplatin and irinotecan.[59] Recent development in targeting therapy initiated the use of antibodies like sorafenib, cetuximab, avastin and octreotide. Sorafenib can be taken orally and act mainly by targeting the proteins which help tumor to grow.[60]

CONCLUSION

Hepatic carcinoma has become an enormous burden on global health care sector and a major cause of morbidity and mortality since 1980. Pathogenesis of HCC is multifactorial in origin and usually diagnosed at an advanced stage, so management solely depends on the stage, liver function and overall health status of individuals and in short requires multidisciplinary approach. Liver transplantation, liver resection, ablation and embolization are the options available during early stage of HCC, whereas at advance stage, chemotherapy either alone or in combination with sorafenib is used, but survival rate is less than 30%. Hence there is a need to have a regular and timely checkup and necessary precaution has to be taken besides continuously looking out for a newer novel drug therapy.

Conflict of interest: Nil.

REFERENCES

1. Alison MR. Liver stem cells: implications for hepatocarcinogenesis. Stem Cell Rev. 2005; 1(3): 253-260.
2. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology. 2012; 142: 1264–1273.
3. Motola-Kuba D, Zamora-Valdes D, Uribe M, Mendez-Sanchez N. Hepatocellular carcinoma. An overview. Ann. Hepatol. 2006; 5: 16–24.
4. Seeff LB. Introduction: The burden of hepatocellular carcinoma. Gastroenterology. 2004; 127(5 Suppl 1): 1-4.
5. Farber E, Solt D, Cameron R, Laishes B, Ogawa K, Medline A. Newer insights into pathogenesis of liver cancer. Am. J. Pathol. 1977; 89: 477–482.
6. Tennant BC, Toshkov IA, Peek SF, Jacob JR, Menne S, Hornbuckle WE, Schinazi RD, Korba BE, Cote PJ, Gerin JL Gastroenterology. 2004; 127(5 Suppl 1): 283-293.
7. Lu MJ, Yao X, Xu Y, et al. Combination of an antiviral drug and immunomodulation against hepadnaviral infection in the woodchuck model. J. Virol. 2008; 82: 2598–2603.
8. Kumar V, Fausto N, Abbas A (editors). Robbins & Cotran Pathologic Basis of Disease (7th ed.). Saunders. 2003; 914–7. ISBN 978-0-7216-0187-8.
9. Wong JB, McQuillan GM, McHutchison JG, et al. Estimating future hepatitis C morbidity, mortality, and costs in the United States. Am J Public Health. 2000; 90(10): 1562-1590.
10. Bosch FX, Ribes J, Diaz M, et al. Primary liver cancer: worldwide incidence and trends. Gastroenterology. 2004; 127(5 Suppl 1): 5-16.
11. Beasley RP, Hwang LY, Lin CC, et al. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22707 men in Taiwan. Lancet. 1981; 2(8256): 1129-1133.
12. Chien-Jen Chen; Hwai-I. Yang; Jun Su; Chin-Lan Jen; San-Lin You; Sheng-Nan Lu; Guan-Tarn Huang; Uchenna H. Iloeje. "Risk of Hepatocellular Carcinoma Across a Biological Gradient of Serum Hepatitis B Virus DNA Level". JAMA. 2006; 295(1): 65–73.
13. Zhang X, Zhang H, Ye L. Effects of hepatitis B virus X protein on the development of liver cancer. J Lab Clin Med. 2006; 147(2): 58-66.
14. McKillop IH, Moran DM, Jin X, et al. Molecular pathogenesis of hepatocellular carcinoma. J Surg Res. 2006; 136(1): 125-135.
15. Kulik LM, Mulcahy MF, Omary RA, et al. Emerging approaches in hepatocellular carcinoma. J Clin Gastroenterol. 2007; 41(9): 839-854.
16. Watanabe S, Horie Y, Kataoka E, et al. Non-alcoholic steatohepatitis and hepatocellular carcinoma: lessons from hepatocyte-specific phosphatase and tensin homolog (PTEN)-deficient mice. J. Gastroenterol. Hepatol. 2007; 22: 96–100.
17. Lu JW, Ho YJ, Yang YJ, Liao HA, Ciou SC, Lin LI, Ou DL. Zebrafish as a disease model for studying human hepatocellular carcinoma. World J Gastroenterol, 2015; 21(42): 12042-12058.
18. http://www.hopkinsmedicine.org/liver_tumor_center /conditions/benign_tumors_cysts.html (visited on 1-8-2016).
19. Jarvelainen HA, Lukkari TA, Heinaro S, Sippel H, Lindros KO. The antiestrogen toremifene protects against alcoholic liver injury in female rats. J Hepatol. 2001; 35(l): 46–52.
20. Hwang, S.J., Tong, M.J., Lai, P.P., Ko, E.S., Co, R.L., Chien, D. Kuo, G. Evaluation of hepatitis B and C viral markers (clinical significance in Asian and Caucasian patients with hepatocellular carcinoma in the United States of America). J Gastroenterol Hepatol. 1996; 11: 949–954.
21. http://www.hepatitisc.uw.edu/go/evaluation-staging-monitoring/natural-history/core-concept/all (visited on 1-8-2016).
22. Jepsen P, Ott P, Andersen PK, Sorensen HT, Vilstrup H. Risk for hepatocellular carcinoma in patients with alcoholic cirrhosis: a Danish nationwide cohort study. Ann Intern Med. 2012; 156(12): 841–847.
23. Hui-Tzu Hsu, Chin-Wen Chi. Emerging role of the peroxisome proliferator-activated receptor-gamma in hepatocellular carcinoma Journal of Hepatocellular Carcinoma, 2014: 1: 127–135.
24. Marrero, J. A., Fontana, R. J., Su, G. L., Conjeevaram, H. S., Emick, D. M. and Lok, A. S., NAFLD may be a common underlying liver disease in patients with hepatocellular Carcinoma in the United States. Hepatology, 2002; 36: 1349–1354.
25. http://slideplayer.com/slide/3359757/ (visited on 1-8-2016).
26. Deutsch M, Papatheodoridis GV, Tzakou A, Hadziyannis SJ. Risk of hepatocellular carcinoma and extrahepatic malignancies in primary biliary

cirrhosis. Eur J Gastroenterol Hepatol. 2008; 20: 5-9.
27. Donato, F., Tagger, A., Chiesa, R., Ribero, M.L., Tomasoni, V., Fasola, M., Gelatti, U., Portera, G., Boffetta, P., Nardi, G. Hepatitis B and C virus infection, alcohol drinking, and hepatocellular carcinoma (a case-control study in Italy) . Brescia HCC Study. Hepatology. 1997; 26: 579–584.
28. https://www.dreamstime.com/royalty-free-stock-photos-alcoholic-liver-disease-image24832798 (visited on 1-8-2016).
29. Lagiou, P., Kuper, H., Stuver, S.O., Tzonou, A., Trichopoulos, D., Adami, H.O. Role of diabetes mellitus in the etiology of hepatocellular carcinoma. J Natl Cancer Inst. 2000; 92: 1096–1099.
30. Møller H, Mellemgaard A, Lindvig K, Olsen JH. Obesity and cancer risk: a Danish record-linkage study.Eur J Cancer. 1994; 30A: 344–350.
31. Welzel TM, Graubard BI, Zeuzem S, El-Serag HB, Davila JA, McGlynn KA. Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. Hepatology. 2011; 54: 463–471.
32. http://atlasofscience.org/fatty-liver-disease-a-condition-caused-by-modern-day-lifestyle/ (visited on 1-8-2016).
33. Wogan GM. Aatoxin exposure as a risk factor in the etiology of hepatocellular carcinoma. In: Okuda K, Tabor E (eds). Liver Cancer. Churchill, Livingstone, New York, 1997; 3: 1 1-8.
34. Triger DR, Millward-Sadler GH, Czaykowski AA, Trowell J, Wright R. Alpha-1-antitrypsin deficiency and liver in adults. Q J Med. 1976; 45(178): 51–72.
35. Solis, JA. Betancor, P, Campos, R, De Salamanca, R. E., Rojo, P., Marin, I. and Schüller, A. association of porphyria cutanea tarda and primary liver cancer: report of ten cases. the journal of dermatology. 1982; 9: 131–137.
36. Wilkinson ML, Portmann B, Williams R. Wilson's disease and hepatocellular carcinoma: possible protective role of copper. Gut. 1983; 24: 767–771.
37. Kew, M.C., Song, E., Mohammed, A., Hodkinson, J. Contraceptive steroids as a risk factor for hepatocellular carcinoma (a case/control study in South African black women). Hepatology. 1990; 11: 298–302.
38. Thorotrast induced hepatic cholangiocarcinoma and angiosarcoma.Winberg CD, Ranchod M.Hum Pathol. 1979; 10(1): 108-112.
39. Mastrangelo, Giuseppe, Fedeli Ugo, Fadda Emanuela, Valentini Flavio, Agnesi Roberto, Magarotto Giancarlo, Marchi Teresio, Buda Andrea, Pinzani Massimo, and Martines Diego. "Increased Risk of Hepatocellular Carcinoma and Liver Cirrhosis in Vinyl Chloride Workers: Synergistic Effect of Occupational Exposure with Alcohol Intake." Environmental Health Perspectives. 2004; 11: 1188-1192.
40. Lander JJ, Stanley RJ, Sumner HW, Boswell DC, Aach RD. Angiosarcoma of the liver associated with Fowler's solution (potassium arsenite). Gastroenterology., 1975; 68(6): 1582–1586.
41. Llovet JM, Fuster J, Bruix J. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. Liver Transpl. 2004; (2 Suppl 1): 115-120.
42. Kemmer N, Neff G, Kaiser T, et al. An analysis of the UNOS liver transplant registry: high serum alpha-fetoprotein does not justify an increase in MELD points for suspected hepatocellular carcinoma. Liver Transpl. 2006; 12(10): 1519-1522.
43. Colli A, Fraquelli M, Casazza G, et al. Accuracy of ultrasonography, spiral CT, magnetic resonance and alpha-fetoprotein in diagnosing hepatocellular carcinoma: a systematic review. Am J Gastroenterol. 2006; 101(3): 513-523.
44. Ohn T, Garden O. Needle track seeding of primary and secondary liver carcinoma after percutaneous liver biopsy. HPB Surg, 1993; 6: 199–204.
45. Kaido T, Mori A, Ogura Y, Hata K, Yoshizawa A, Iida T, et al. Living donor liver transplantation for recurrent hepatocellular carcinoma after liver resection. Surgery. 2011; 11: 2724–2736.
46. Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. Surgery. 1991; 110(4): 726-734.
47. Onaca N, Davis GL, Jennings LW, Goldstein RM, Klintmalm GB. Improved results of transplantation for hepatocellular carcinoma: a report from the International Registry of Hepatic Tumors in Liver Transplantation. Liver Transpl. 2009; 15(6): 574-580.
48. Marelli L, Stigliano R, Triantos C, et al. Treatment outcomes for hepatocellular carcinoma using chemoembolization in combination with other therapies. Cancer Treat Rev. 2006; 32(8): 594-606.
49. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology. 2003; 37(2): 429-442.
50. D. Coldwell, B. Sangro, H. Wasan, R. Salem, A. Kennedy General selection criteria of patients for radioembolization of liver tumors: an International Working Group report Am J Clin Oncol. 2011; 34: 337–334.
51. Lencioni R, Crocetti L. A critical appraisal of the literature on local ablative therapies for hepatocellular carcinoma. Clin Liver Dis. 2005; 9(2): 301-314.
52. Martin AP, Goldstein RM, Dempster J, et al. Radiofrequency thermal ablation of hepatocellular carcinoma before liver transplantation--a clinical and histological examination. Clin Transplant. 2006; 20(6): 695-705.
53. Claudio Amabile, Laura Farina, Vanni Lopresto, Rosanna Pinto, Simone Cassarino, Nevio Tosoratti, S. Nahum Goldberg, Marta Cavagnaro. Tissue shrinkage in microwave ablation of liver: an ex vivo predictive model. International Journal of Hyperthermia, 2016; 24: 1-9.

54. Hui Huang, Ping Liang, Xiao-ling Yu, Zhi-gang Cheng, Zhi-yu Han, Jie Yu, Fang-yi Liu. Safety assessment and therapeutic efficacy of percutaneous microwave ablation therapy combined with percutaneous ethanol injection for hepatocellular carcinoma adjacent to the gallbladder. International Journal of Hyperthermia. 2015; 31: 40-47.
55. Murray-Lyon IM, Parsons VA, Blendis LM, Dawson JL, Rake MO, Laws JW, Williams R. Treatment of secondary hepatic tumours by ligation of hepatic artery and infusion of cytotoxic drugs. Lancet. 1970; 25; 2(7665): 172–175.
56. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized Phase III study. J Clin Oncol. 2001; 19: 2282–2229.
57. Ishikawa T, Utoh M, Sawada N, et al. Tumor selective delivery of 5-fluorouracil by capecitabine, a new oral fluoropyrimidine carbamate, in human cancer xenografts. Biochem Pharmacol. 1998; 55: 1091–1097.
58. Leung TW, Patt YZ, Lau WY, et al. Complete pathological remission is possible with systemic combination chemotherapy for inoperable hepatocellular carcinoma. Clin Cancer Res. 1999; 5: 1676–1681.
59. J. M. Llovet, S. Ricci, V. Mazzaferro et al. "Sorafenib in advanced hepatocellular carcinoma," The New England Journal of Medicine, 2008; 4: 378–390.
60. Binato M, Kruel Schmidt M, Silveira Volkweis B, Behrend Silva Ribeiro G, Isabel Edelweiss M, Ricachenevsky Gurski R. Mouse model of diethylnitrosamine-induced gastric cancer. J. Surg. Res. 2008; 148(2): 152–157.