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Review Article

A SYSEMATIC REVIEW ON PATHOLOGY AND MANAGEMENT OF HEPATOCELLULAR CARCINOMA

Jaiswal Gourav*, Khan Foziya, Agarwal Alka

U.S. Ostwal Institute of Pharmacy, Mangalwad, Rajasthan, India 312024

Now a day's cancer is the most prevalent life threatening disease which is spreading because of the lifestyle we are living. Cancer is due to uncontrolled growth of cell which can be cured if diagnosed in early stage of life. Treatment of cancer depends on the various internal and external factors causing cancer. Cancer is screened by different screening test and a number of treatments are now available these days such as gene therapy, chemotherapy, surgery, radiation therapy, immunotherapy etc. In future up to 2030 around 22.2 million cases are expected to be diagnosed for cancer. Primary liver cancer (PLC) is one of the most common malignancies worldwide with increasing incidence and accounts for the third leading cause of cancer-related mortality. Traditional morphopathology primarily emphasizes qualitative diagnosis of PLC, which is not sufficient to resolve the major concern of increasing the long-term treatment efficacy of PLC in clinical management for the modern era.

Keywords: Liver cancer, Hepatocellular carcinoma, Intrahepatic cholangiocarcinoma, Practice guidelines, Pathology, Diagnosis, primary liver cancer, hepatocellular carcinoma, cholangiocarcinoma

INTRODUCTION

Cancer is one of the most feared diseases in the world and it affects over 11 lakh people every year in India alone**.** Worldwide, more than 10 million people succumb to this disease every year. Let us explore what is cancer, the causes of cancer, symptoms, diagnosis, and treatment of cancer. In humans, cell differentiation and proliferation are highly manipulated and regularized by the cell division mechanism. Uncontrolled cell division occurs when a process called contact inhibition fails. In healthy organisms, during this process, when cells come in contact with other cells, the process of cell replication ceases.As a result, contact inhibition becomes a powerful anti-cancer mechanism, but it is lost in cancer cells. Hence, most types of cancer have tumours (except for cancers of the blood) [1,2]

It is often presumed that all tumours are cancerous – but this is a misconception. A tumour becomes cancer

Hepatocellular carcinoma is the most common form of primary liver cancer in the United States with three-quarters of primary and secondary liver cancer cases. The trend for both estimated new and instances of death are increasing in parallel to the geographical underlying chronic liver disease or cirrhosis etiology.

From a medical perspective, cancer types can be classified based on the type of cell they originated from. Therefore cancer can be classified into: Carcinoma, The most common

form of cancer, it originates from the epithelial cells Sarcoma Originates from the connective tissues such as cartilage, fat and bone tissues.Melanoma Originates from melanocytes, which are a type of cell that contains pigments. Lymphoma & Leukaemia Originates from the cells that comprise blood (such as b lymphocytes or white blood cells) [3,4]

Liver cancer

Primary liver cancer is a disease in which malignant (cancer) cells form in the tissues of the liver. Cancer that forms in other parts of the body and spreads to the liver is not primary liver cancer. The liver is one of the largest organs in the body. It has two lobes and fills the upper right side of the abdomen inside the rib cage. The main functions of the liver include the following:

- To make bile to help digest fat that comes from food
- To store glycogen (sugar), which the body uses for energy
- To filter harmful substances from the blood so they can be passed from the body in stools and urine.

Types of liver cancer

Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma is also called hepatoma or HCC. It's the most common type of primary liver cancer. Because of this, the information in this primary liver cancer section is mostly about hepatocellular carcinoma. [5,6]

Fibrolamellar carcinoma

Fibrolamellar carcinoma tends to develop in people in their 20's or 30's. It's not usually linked with cirrhosis or infection with hepatitis B or C.

Some people with other types of liver cancer can have high levels of a chemical called alpha fetoprotein (AFP) in their blood. This is usually not the case for people with fibrolamellar carcinoma.

Bile duct cancer (cholangio carcinoma)

Cholangio refers to the bile ducts, so cholangiocarcinoma is cancer of the bile ducts. The major bile ducts are tubes that connect the liver and gallbladder to the small bowel. The bile ducts carry bile, which is made by the liver. Bile helps to digest fats in food.

Angiosarcoma

Angiosarcoma is also known as haemangiosarcoma. It's a type of cancer called a soft tissue sarcoma. [7.]

Benign liver growths (non cancerous growths)

Most growths (tumours) in the liver are benign. They aren't cancer and won't become cancerous (malignant) in the future.

The most common types of benign tumours in the liver are:

- haemangioma
- hepatic adenoma
- focal nodular hyperplasi[8]

Pathology

Macroscopically, liver cancer appears as a nodular or infiltrative tumor. The nodular type may be solitary (large mass) or multiple (when

developed as a complication of cirrhosis). Tumor nodules are round to oval, gray or green (if the tumor produces bile. Histologically .HCC is graded as well as moderately or poorly differentiated. Direct hepatotoxicity by ethanol-hapatotxicity by ethanol metabolites-oxidative stress-immunological mechanism- inflammation-fibrogenesis– increase redox ratio.[9]

Due to etiological factor

Genomic DNA damage occurs

Loss of cellular growth controls, (mutation take place)

Diagnosis

Angiosarcoma, Cirrhosis, Cholangiocarcinoma, Epithelioid, hemangioendothelioma-Embryona ,sarcoma, Hepatoblastoma, Hepatocellular carcinoma, Hemangiomas- Hamartom, Biopsy, Histopathological studies of tissue, Radiography technique, Computed tomography, Magnetic resonance imagine, Molecular biology techniques [10]

Risk and Factor

Getting Older, Liver Cirrhiosis, Smoking, Body Weight-Alcohol, Infection with hepatitis virus Diabetes, HIV and AIDS.) , Aflotoxin, Chemical, Family history, Liver flukes, Gall stone and gallbladder.[11,12]

Stage

Staging looks at the size of the cancer (tumour) and whether it has spread anywhere else in the body. There are different staging systems that doctors can use for liver cancer. The Number staging system is one of these. It divides liver cancer into 4 main stages, from **1 to 4**[13,14]

Stage 1A: means there is a single tumour in the liver that is 2cm or less, and it has not grown into the blood vessels.

Stage 1B: means there is a single tumour that is more than 2cm, and it has not grown into the blood vessels.

Stage 2: liver cancer means that there is a single tumour that is more than 2 cm, and it has grown into blood vessels of the liver.

Stage 3A: There is more than one tumour, and at least one of them is larger than 5cm. At this stage the cancer has not spread to the lymph nodes or any other part of the body.

Stage 3B The cancer has grown into one of the main blood vessels of the liver (the portal vein or hepatic vein).

Stage 4A: The cancer is any size and there may be more than one tumour. It may have grown into blood vessels or the organs around the liver. It has spread to lymph nodes but not to other parts of the body.

Stage 4B: The cancer is any size and there may be more than one tumour. It may have grown into blood vessels or the organs around the liver. It may or may not have spread into lymph nodes, but has spread to another part of the body such as the lungs or bones.

Liver-specific contrast agents

Hepatocyte-selective contrast agents: Hepatocyte-selective contrast agents undergo uptake by hepatocytes and are eliminated through renal and biliary excretion. All are T_1-

relaxation enhancing agents and increase the signal intensity in normal liver tissue and hepatocyte containing tumors.

Reticuloendothelial gents:

Reticuloendothelial agents target the RES, particularly the liver and spleen and reflect the number of functioning macrophages Reticuloendothelial agents currently in clinical use include superparamagnetic iron oxide (SPIO) particles. SPIO particles act as a negative contrast agent and can be used alone or in combination with gadolinium..

Diffusion-weighted MRI: Diffusion-weighted imaging (DWI) uses pulse sequence techniques that are sensitive to the very small scale motion of water protons at a microscopic level and improves the conspicuity of many hepatic and extrahepatic tumors. [15]

Diagnosis

Imaging plays a critical role in HCC diagnosis. HCC lesions are brighter than the surrounding liver in the arterial phase in a CT scan or MRI and less bright than the surrounding parenchyma in the venous and delayed phases and this is due to the differential blood supply of the tumor compared with the background liver. [16,17]

This phenomenon of 'arterial enhancement and delayed washout' has a sensitivity of 89% and a specificity of 96% for HCC and is regarded as the radiological hallmark of HCC. In patients with liver cirrhosis the presence of these typical vascular hallmarks identified by quadruple-phase CT or dynamic contrast-enhanced MRI is sufficient for diagnosis without requiring histological confirmation

A more recent radiological approach, the LI-RADS (Liver Imaging Reporting and Data System) assigns lesions > 10 mm to different categories reflecting the relative probability of the lesion of being benign, HCC, or other hepatic malignant neoplasm according to an enlarged the number of criteria (arterial phase enhancement, tumor size, washout, enhancing capsule and threshold growth features) . AFP and other serum biomarkers generally have a minor role in the diagnosis of HCC.[18]

TREATMENT FOR LIVER CANCER

Surgical Resection (Partial Hepatectomy)

Surgical resection is the mainstay treatment for solitary HCCs in patients with preserved liver function. With recent advances in laparoscopic liver resection, with a reduction in operative blood loss, operation time, and length of hospital stay, the surgical outcome is comparable to open hepatectomy in a selected population.

Adjuvant Therapy after Surgical Resection Adjuvant therapy after HCC resection holds promising potential as it may eradicate residual cancer cells and prevent secondary liver carcinogenesis. Currently, the conclusive role of adjuvant therapy following curative resection of HCC remains to be defined. Nevertheless, several adjuvant strategies have been tested in clinical trials, including systemic and intra-arterial chemotherapy, intra-arterial

radio labeled lipiodol, TACE, acyclic retinoids, interferon, adoptive immunotherapy, autologous tumor vaccine.

Liver Transplantation

Liver transplantation has the advantage of correcting the underlying cirrhosis, reducing the risk of postoperative liver failure, and has been generally considered the treatment of choice for patients with early-stage HCC with moderate to severe cirrhosis. Selective criteria for liver transplantation, known as the Milan criteria, were first introduced by Mazzaferro et al. and included a single tumor ≤5 cm or no more than three multiple tumors with the largest ≤3 cm in diameter, and no evidence of macrovascular involvement or extrahepatic disease. Showed 4-yr overall and recurrence-free survival rates of 85% and 92% in HCC patients who met the Milan criteria and underwent liver transplantation.

Locoregional Therapy

Locoregional ablative therapy, including ethanol injection, radiofrequency ablation, and cryotherapy, can be the primary treatment for selected inoperable patients with HCC confined to the liver, but can also be used as a bridge to liver transplantation or as a palliative procedure to extend disease-free survival.

Liver Cancer: Latest Research

Cancer vaccines: are treatments that may help the immune system recognize and attack hepatocellular carcinoma (HCC) cells. Sometimes the vaccine is given with an immune system stimulant, such as sargramostim (Leukine, Prokine)

Combining systemic cancer medications: Different drugs destroy cancer cells in different ways. Using a combination of drugs can increase the chance that more cancer cells will be destroyed. Many times, 1 drug will help another drug work better.

Combining therapies.

Researchers are looking into whether combining treatments, such as radiofrequency ablation (RFA) and chemoembolization, is more effective than using these treatments separately.

- **Anti-angiogenesis drugs.** In addition to sorafenib and regorafenib, which are discussed in Types of Treatment, several other anti-angiogenic drugs are being studied in clinical trials.
- **Greater use of liver transplantation.** Researchers are investigating the possibility of expanding the criteria for liver transplantation for HCC. This would make more patients eligible for the procedure.
- **Gene therapy.** This new treatment changes a gene to fight cancer. Although gene therapy is in the very early stages of development, some clinical trials are already underway. In 1 example, the new gene makes chemotherapy work better. In this type of treatment, a gene can be directly injected into the tumor.
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- **Palliative care/supportive care.** Clinical trials

are underway to find better ways of reducing symptoms and side effects of current HCC treatments to improve comfort and quality of life for patients[19-22]

CONCLUSION

Hepatocellular carcinoma is potentially curable if discovered in its initial stages. Medical staff should be familiar with strategies for early diagnosis and treatment of hepatocellular carcinoma as a way to decrease mortality associated with this malignant neoplasm. Treatment of liver cancer is a multidisciplinary and multimodel treatment approach with options that are chosen generally on an individualized patient basis according to the complex interplay of tumor stage and the extent of underlying liver disease, as well as patient performance status. Future efforts on the development of better predictive, diagnostic, and prognostic biomarkers of HCC as well as molecularly targeted therapy may improve the overall survival of patients with HCC across stages.

REFERENCE

1. Arias-Flórez JS, Martínez-Delgado AM, Alarcón-Tarazona ML, Insuasty-Enrique JS, Díaz-Martínez LA. [Conventional serum tumor markers in liver cancer. Rev Med Chil. 2018 Dec; 146(12):1422-28.

2 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics 2012. CA Cancer J Clin. 2015; 65: 87–108.

3 Parizadeh SM, Jafarzadeh-Esfehani R, Ghandehari M, Goldani F, Parizadeh SMR,Hassanian SM, Ghayour-Mobarhan M, Ferns GA, Avon A. MicroRNAs as Potential Diagnostic and Prognostic Biomarkers in Hepatocellular Carcinoma. Curr Drug Targets. 2019; 20(11): 1129-40.

4. Sayiner M, Golabi P, Younossi ZM. Disease Burden of Hepatocellular Carcinoma: A Global Perspective. Dig Dis Sci. 2019 Apr 64(4):910-17.

5. Textbook of Uncommon Cancers (5th edition) D Raghavan, MS Ahluwalia, CD Blanke and others Wiley Blackwell, 2017.

6. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and followup AVogelandothers Annals of Oncology, 2018. Volume 29, Supplement 4, Pages 238-55

7. Cancer: Principles and Practice of Oncology (11th edition) VT DeVita, TS Lawrence, SA Rosenberg Wolters Kluwer, 2019

8. Hepatocellular carcinoma JM Llovet and others National Reviews Disease Primers, 2021. Volume 21;7(1), Pages 1 – 28

9. Systemic treatment of hepatocellular carcinoma: An EASL position paper J Bruix and others Journal of Hepatology, July 2021. Pages 1-15

10. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans - List of classifications by cancer site International Agency for Research on Cancer (IARC), last updated November 2018

11. Diet,nutrition,physical activity and liver cancer World Cancer Research Fund (WCRF), 2015 . A global view of hepatocellular carcinoma trends, risk, prevention and management

12. Nature reviews of gastroenterology and hepatology, 2019. Volume 16, Number 10, pages 589-604 (risk and csause)

13. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma European Association for the Study of the Liver Journal of Hepatology, 2018. Volume 69, Pages 182-236

14. Puustinen L, Barner-Rasmussen N, Pukkala E, Färkkilä M. Incidence, prevalence, and causes of death of patients with autoimmune hepatitis: A nationwide register-based cohort study in Finland. Dig Liver Dis. 2019 Sep;51(9):1294-99

15. Abdalla EK, Hicks ME, Vauthey JN. 2001. Portal vein embolization: Rationale, technique and future prospects. *Br J Surg* 88 165–75.

16. Abulkhir A, Limongelli P, Healey AJ, Damrah O, Tait P, Jackson J, Habib N, Jiao LR. 2008. Preoperative portal vein embolization for major liver resection: A meta-analysis. *Ann Surg* 247: 49–57Altekruse SF, McGlynn KA, Reichman ME. 2009. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol* 27: 1485–91.

17. Hamm B, Vogl TJ, Branding G, Schnell B, Taupitz M, Wolf KJ, Lissner J. Focal liver lesions: MR imaging with Mn-DPDP--initial clinical results in 40 patients. Radiology. 1992;182:167–74.

18. Ferrucci JT, Stark DD. Iron oxide-enhanced MR imaging of the liver and spleen: review of the first 5 years. AJR Am J Roentgenol. 1990;155:943–950

19.. Chow LC, Bammer R, Moseley ME, Sommer FG. Single breath-hold diffusion-weighted imaging of the abdomen. J Magn Reson Imaging. 2003;18:377–382.

20. van der Pol CB, Lim CS, Sirlin CB, et al.. Accuracy of the liver imaging reporting and data system in computed tomography and magnetic resonance image analysis of hepatocellular carcinoma or overall malignancy - a systematic review. *Gastroenterology* 2019;156: 976-986. j. gastro .2018.11.020 10.1053 / j. gastro .2018.11.

21. J, Sherman M, et al.. LI-RADS (Liver Imaging Reporting and Data System): summary, discussion, and consensus of the LI-RADS Management Working Group and future directions. Hepatology 2015; 61:1056-65.

22. Mitchell DG, Bruix J, Sherman M, Sirlin CB. LI-RADS (Liver Imaging Reporting and Data System): Summary, discussion, and consensus of the LI-RADS Management Working Group and future directions. Hepatology. 2014 Dec 12;61(3):1056–60.