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Review Article

Hepatocellular carcinoma Diagnosis treatment and management

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ABSTRACT

Hepatocellular carcinoma (HCC) is the most prevalent primary liver cancer and the primary cause of cancer-related mortality. HCC ranks as the ninth most common cause of cancer-related fatalities in the US. Incident and death rates are still rising despite improvements in screening, prevention, and diagnosis and treatment technologies. Regardless of the cause, cirrhosis continues to be the primary risk factor for the development of HCC. There are separate risk factors for the development of cirrhosis associated with hepatitis B and C. Since alcohol misuse is five times more common in the US than hepatitis C, alcohol consumption continues to be a significant extra risk factor. Without pathologic confirmation, the diagnosis is confirmed. Screening involves 6-monthly serological indicators like β-fetoprotein as well as radiologic testing including ultrasound, computed tomography, and magnetic resonance imaging. There are several treatment options available, however the only cures are orthotopic liver transplantation (OLT) and surgical resection. HCC typically develops in the context of advanced-stage chronic liver disease, though this is not always the case. Due to the variability of HCC and the occasionally challenging process of confirming hepatocellular distinction, the histological diagnosis of HCC presents numerous obstacles, especially when working with liver biopsy specimens. The spectrum of primary liver cancers includes a variety of tumours exhibiting both hepatocellular and cholangiocellular differentiation, with or without a progenitor/stem cell component present in the center. At either extreme of the spectrum are typical hepatocellular and cholangiocarcinomas. It can be very difficult to characterize combined (or mixed) hepatocellular-cholangiocarcinoma. Differentiating between HCC and its antecedents remains the primary issue for the histopathologist in advanced-stage chronic liver disease; nevertheless, this is rarely critical in the clinical context at this time. HCC originating in non-cirrhotic livers needs to be differentiated from other primary and extrahepatic tumours and from hepatocellular adenoma bearing in mind that progression

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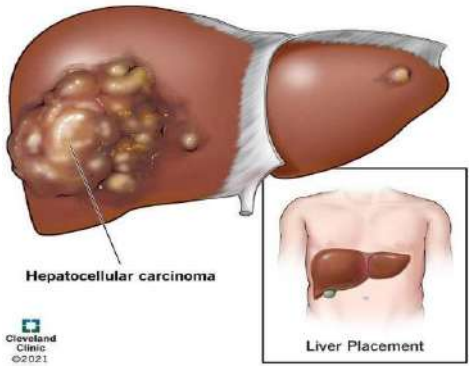
to malignancy is more through a continuum that watertight histological categories

INTRODUCTION

Hepatocellular carcinoma is the most common kind of liver cancer. The most common primary tumour of the condition that, may be fatal, so diagnosis early. Treatment options include



liver transplantation or surgery to remove the malignant cells. [1] After lung and colon carcinomas, hepatocellular carcinoma (HCC) is the most frequent primary tumor of the liver with the third-highest death rate among all solid tumors. HCC still has a worse scenario than other tumor forms, even with ongoing improvements in the way the illness is managed. The only two curative treatment options are surgical excision and orthotopic liver transplantation (OLT) [2

History of hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the primary cause of death for people with cirrhosis and the third most prevalent cause of cancer-related death globally-related symptoms are typically absent. Instead, 80–90% of people with HCC have cirrhosis, which is the underlying illness that most often causes symptoms in patients. As a result, the majority of patients receive an advanced diagnosis, which frequently makes potentially curative therapy unavailable. This has contributed to a 5-year overall survival rate of 12% and a median.[3] HCC is the ninth most common cause of cancer-related fatalities in the US.1 In addition to 21,670 fatalities, a total of 30,640 new cases of liver and intrahepatic bile duct cancer were projected to develop in 2013.The frequency of 2 HCC was greater in Eastern and Southern Asia, Middle and Western Africa, Melanesia, and Micronesia/Polynesia, and it was more common in males than females (2.4:1).3. Among American Indians and Alaskan Natives, the age-adjusted incidence of liver cancer has increased from 1.6 per 100,000 persons to 4.6 per 100,000 individuals. Blacks, Whites, and Hispanics are the next most affected groups.4. A review on hepatocellular carcinoma survival of 6 to 20 months after diagnosis.[4]

Causes of Hepatocellular carcinoma

People who already have chronic (long-lasting) liver cancer may develop hepatocellular carcinoma as a result of alcohol intake, cirrhosis, or hepatitis virus infection. the most prevalent kind of adult liver cancer. Cirrhosis and/or HCC are two outcomes of persistent viral hepatitis. The most prevalent causes of chronic hepatitis worldwide are hepatitis B and C.

- **Cirrhosis**

Cirrhosis, whose main causes are HBV and HCV infection, is the key risk factor for developing HCC. In fact, research suggests that HBV infection accounts for 50% of all HCC cases globally and that HCV infection accounts for another 25%. Long-term chronic liver illness can cause cirrhosis, which is characterized by a decline in hepatocyte proliferation, a sign that the liver's ability for regeneration has been exhausted. This results in an increase in fibrous tissue and the death of liver cells, which creates the ideal environment for the growth of malignant nodules . The presence and severity of liver cirrhosis must be determined in all patients in order to assess prognosis and recommend treatment because it can have a significant impact on liver reserve and is frequently a component of the morbidity and mortality linked to HCC. [5]

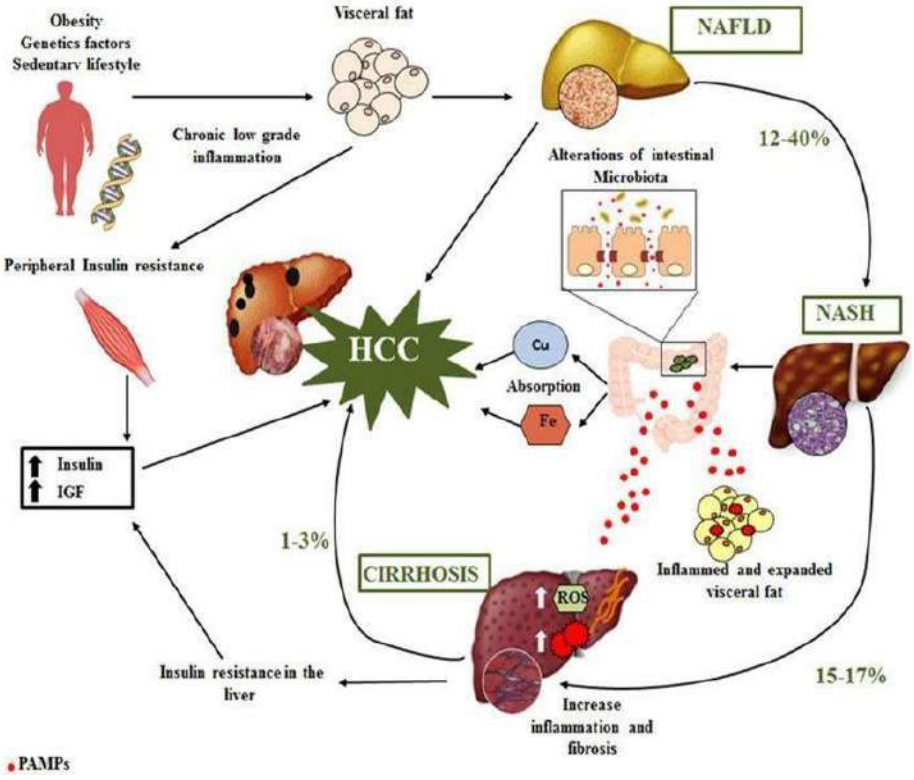
Cases in India

Autopsy Data on HCC in India.

Place	Autopsies (No.)	HCC(%)
Mumbai	6000	0.2
Mumbai	4000	0.2
Agra	1234	1.6
Guntur	629	
Andhra Pradesh	2789	
Chennai	1218	1.9
Bangladesh	5450	0.2
Denmark	14881	0.3
USA(Boston)	14000	0.6
Japan	401,381	3.1
Hong Kong	1480	6.8

The age-adjusted incidence rate of hepatocellular carcinoma (HCC) in India ranges from 0.7 to 7.5 per 100,000 people per year for men and from 0.2 to 2.2 per 100,000 people per year for women, according to the data that are currently available. In India, the male to female ratio for HCC is 4:1. The age of the presenter ranges from 40 to 70. [6]

Mechanism of action of hepacellular carcinoma (Mechanisms/pathophysiology)



Risk factor

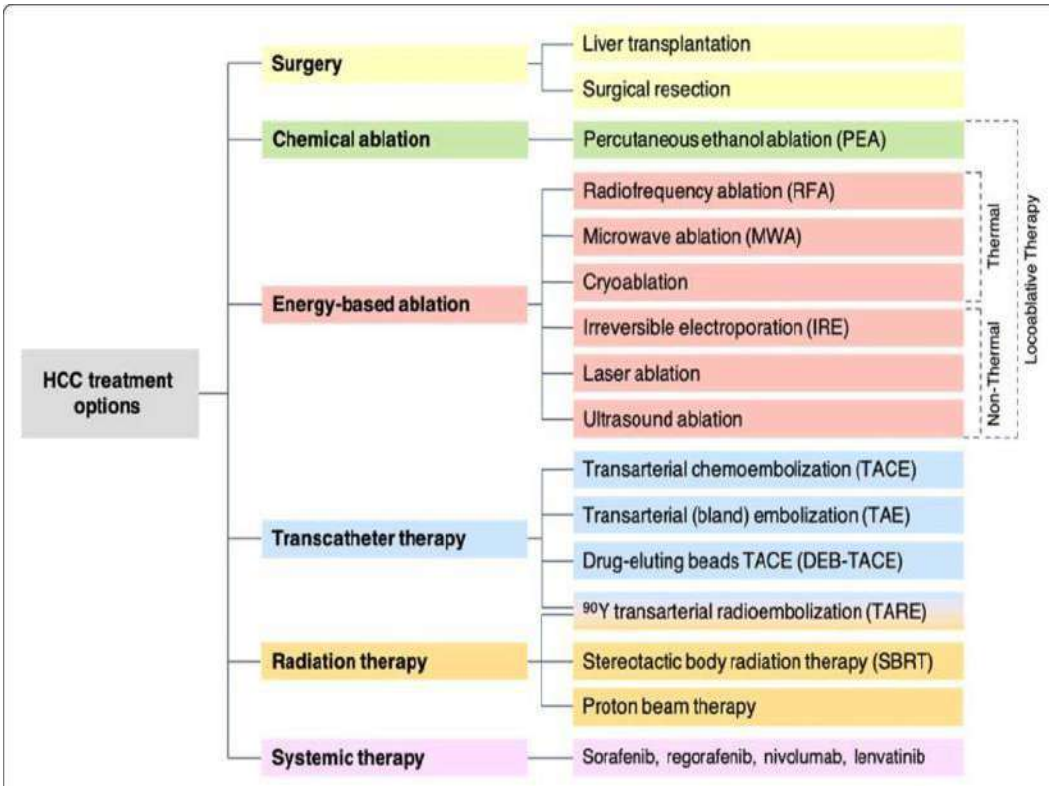
a. Hepatitis B virus infection
b. Hepatitis C virus infection
c. Hepatitis D virus infection
d. Alcohol
e. NASH
f. Age, sex and other factor

Treatment

For those who are unable to undergo surgery, ablation methods that use high heat or cold to eliminate the cancer cells in the liver may be advised. These techniques include cryoablation, radiofrequency ablation, and ablation using alcohol or microwaves. directly administering radiation or chemotherapy to cancer cells

Unfortunately, the diagnosis of HCC is frequently made after the disease is advanced and the patient has developed symptoms and some liver damage. There are essentially no treatments that would

increase survival at this late stage.[7] The BCLC therapy strategy for HCC patients stratifies patients according to their performance status, underlying liver function, and tumor burden to determine the best course of treatment. Curative methods for early-stage HCC include liver transplantation and surgical resection.



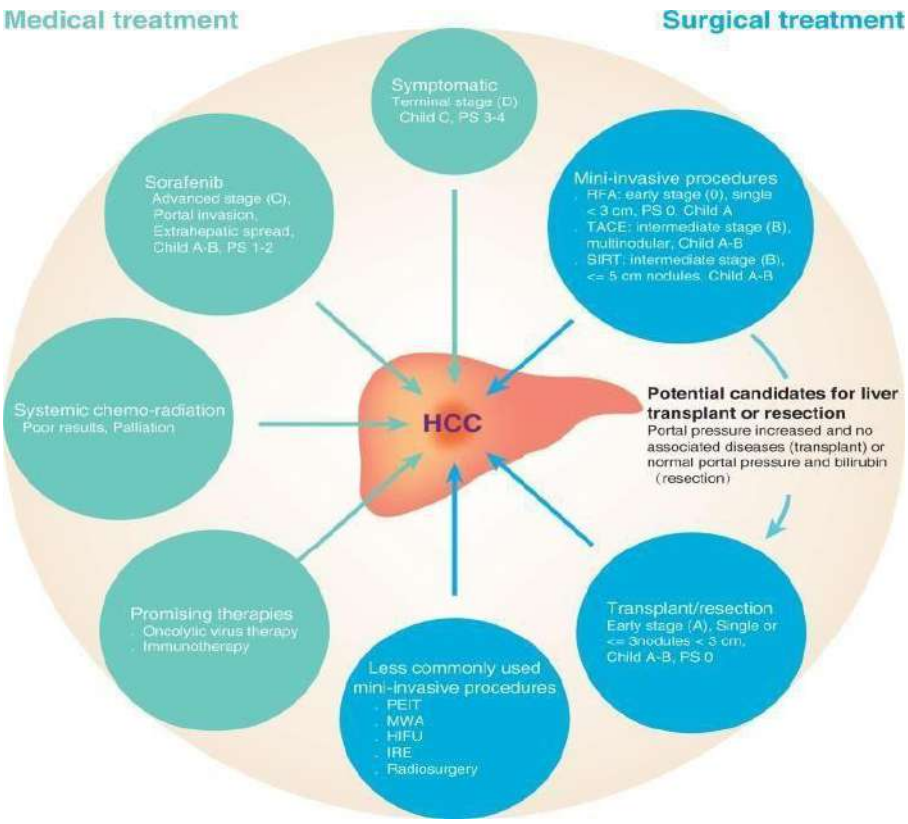
1. Liver transplantation

Because it treats the underlying cirrhosis as well as the hepatocellular carcinoma and is linked to a significantly lower incidence of recurrent cancer compared to alternative treatment approaches, liver transplantation is the best option for treating early stage, unresectable hepatocellular carcinoma in patients with cirrhosis. As the gold standard for patient selection, liver transplantation for hepatocellular carcinoma within the Milan criteria (one lesion between 3 and 5 cm, or two to three lesions between 1 and 3 cm) has long been established. [8]

2. Ablation

When a tumor is less than 3 cm in diameter, ablation is highly effective, but once the tumor is more than 3 cm, its effectiveness falls. There are numerous therapy options for the local ablation of hepatocellular carcinoma, all of which generally produce comparable results. The two most often utilized ablation techniques are radiofrequency ablation and microwave ablation.Through the use of radiofrequency (RFA), microwave, cryotherapy, or chemical injections such as ethanol (percutaneous ethanol injection, PEI), the main goal of this treatment is to cause the necrosis of cancerous cells. When measured, the amount of necrosis brought on by these 2 procedures covers almost 100% of the tumor. One promising method with encouraging response rates is microwave ablation.[9]

3. Surgical treatment



Available drug in market

Drugs Approved for Liver Cancer

- Atezolizumab.
- Avastin (Bevacizumab)
- Bevacizumab.
- Cabometyx (Cabozantinib-S-Malate)
- Cabozantinib-S-Malate.
- Cyramza (Ramucirumab)
- Durvalumab.
- Futibatinib.

New drug for HCC

- sorafenib
- Nivolumab plus ipilimumab
- Lenvatinib
- Regorafenib

Adverse effect of Nivolumab

Nivolumab was well tolerated, only one severe adverse effect was reported and antitumor activity was observed . In September 2017, FDA approved nivolumab for the treatment of HCC in patients previously treated with sorafenib o link to this article:

Clinic Liver Cancer

For patients with intermediate stage HCC, particularly those with large or multinodular HCC, well-preserved liver function, and no signs of vascular invasion or extrahepatic dissemination, transarterial chemoembolization (TACE) is the first-line treatment. Since 2004, the terms conventional TACE (cTACE) and TACE with drug-eluting beads (DEB- TACE) have been used interchangeably. First-line treatment for HCC patients with intermediate stage was cTACE. It combines an embolizing agent and a lipid-based emulsion for transcatheter chemotherapy delivery to provide potent cytotoxic and ischemia effects.

Drug-eluting beads (DEBs) were created to prolong and intensify ischemia while also gently releasing chemotherapy drugs. Both early stage patients (those with a single nodule or up to three nodules < 3 cm) and certain late stage patients can now receive TACE treatment thanks to recent

advancements. Here, we examine new clinical data that support the use of TACE for patients with early-stage, intermediate-stage, and advanced-stage HCC. This international expert panel suggests a revised TACE algorithm based on the 2014 Raoul et al. TACE algorithm and offers insights into TACE use for patients at any HCC stage.[11]

Clinical trial stydy of new drug for hepatocellular carcinoma

- **Lenvatinib**

The primary systemic therapeutic medication for advanced HCC targets VEGFR 1-3, FGFR 1-4, PDGFR, RET, and KIT . A randomised phase III trial (REFLECT) showed lenvatinib to be noninferior to sorafenib in terms of OS in 2018. Lenvatinib's median overall survival (OS) was 13.6 months while sorafenib's was 12.3 months.

- **Atezolizumab plus bevacuzumab**

Based on the findings of the IMbrave150 trial (NCT03434379), the FDA approved the combination strategy of bevacizumab (anti-VEGF antibody) and atezolizumab (anti-PD-L1 antibody) as the first-line treatment for unresectable HCC in 2020. In this phase III trial, 501 patients with HCC who had not previously received systemic therapy were compared to the effectiveness of bevacizumab coupled with atezolizumab against sorafenib.Bevacizumab in conjunction with atezolizumab therapy was therefore found to be generally safe for HCC patients.

- **Regorafenib**

The FDA originally approved regorafenib in April 2017 as a second-line therapy for patients with advanced HCC who progressed after receiving sorafenib . A multikinase inhibitor called regorafenib primarily targets angiogenic factors such VEGFR1-3, PDGFR-, FGFR1, KIT, RET, and BRAF. Sorafenib's inhibitory action is stronger than that of regulatorafenib . According to the findings of a phase III randomised, placebo-controlled trial conducted in 2017 (NCT01774344), regorafenib was more effective than the placebo, reducing mortality by 37% (median survival of 10.6 months for regorafenib against 7.8 months for placebo). It should be noted that in order to lessen the influence of deteriorating liver function on the study results, this trial exclusively enrolled patients with Child-Pugh A liver function.

- **Cabozantinib**

Cabozantinib is a multitarget tyrosine kinase inhibitor (TKI) with effects on VEGFR1/3, RET, KIT, and AXL in addition to blocking MET and VEGFR2 primarily . Its approval was predicated on a randomised, placebocontrolled phase III trial (CELESTIAL) that demonstrated that the cabozantinib group's median survival was increased by 2.2 months). In instance, the median survival in the cabozantinib group was 11.3 months. among patients who had previously only received sorafenib. This result demonstrated the benefit of cabozantinib as a second-line treatment over sorafenib alone in terms of patient survival (median survival of 10.7 months). Additionally, as seen in previously published research, cabozantinib has the potential to partially alleviate the issue of MET-induced sorafenib resistance [18]

- **Ramucirumab**

Ramucirumab is a monoclonal antibody (mAb) made from recombinant IgG1 that targets VEGFR2 in particular. A randomised phase III trial (REACH) investigating ramucirumab as second-line therapy for patients with advanced HCC was finished by Zhu et al. in 2015 . Sadly, they were unable to get the desired result. Interestingly, they discovered that an elevated baseline level of AFP (400 ng/mL) correlated to longer survival with ramucirumab treatment, despite the fact that a high level of - fetoprotein (AFP) predicts a poor prognosis As a result, ramucirumab was tested again in the REACH-2

study with the new inclusion threshold of AFP 400 ng/mL.Ramucirumab was approved by the FDA as a second-line treatment for patients with HCC whose AFP level was less than 400 ng/mL as a consequence of the first biomarker-based trial with positive findings in HCC.

- **Nivolumab**

One of the crucial immunological checkpoints, nivolumab PD-1, is substantially expressed in worn-out T cells, B cells, and myeloid cells . Based on encouraging outcomes from a phase I/II open-label, noncomparative dose escalation and expansion experiment, in 2017. One of the crucial immunological checkpoints, PD-1, is abundantly expressed in myeloid, B, and fatigued T cells . Based on encouraging findings from a phase I/II openlabel, noncomparative dose escalation and expansion experiment, in 2017 [11]

Novel Immunotherapeutic Approches

The immune system is crucial in preventing the spread of cancer16. Effective anticancer immune surveillance is made possible by the interaction of the innate and adaptive immune systems. Immune evasion is caused by dysfunctional interactions between the immune system and the cancer, which can result in poor antigen recognition or an immunosuppressive tumour microenvironment (TME). Epigenetic and post-transcriptional silencing, changes in the antigen-presenting or peptide-processing machinery, and reduced recognition of tumour- associated antigens (TAAs) by immune cells are all possible causes of reduced TAA recognition by immune cells18. Accumulation of immune cells with poor regulatory function, such as regulatory T cells (Treg), inhibitory B cells, myeloid-derived suppressor cells (MDSCs), or M2-polarized tumor-associated macrophages (TAMs), can result in the existence of an immunosuppressive TME. Co-inhibitory lymphocyte signals, such as immune checkpoint ligands and receptors, are upregulated. Other co-inhibitory lymphocyte signals include reduced immunoglobulin-mediated opsonization, increased levels of tolerogenic enzymes like indoleamine 2,3- dioxygenase-1 (IDO) or arginase-1, and the presence of a metabolically unfavourable environment for immune cells19. Any effort to get over these obstacles to the immune system's ability to effectively kill cancer cells qualifies as an immunotherapy that should be put through a therapeutic review

- **The immune microenvironment of HCC**

Antigenicity of HCC. Expression of tumour antigens is the first stage in the establishment of a T cell response specific for a particular cancer. Deregulated expression of oncofetal and cancer testis antigen genes during hepatocarcinogenesis may trigger a spontaneous immune response25. Blood and tumour samples from individuals with HCC25 can be used to identify naturally existing CD8+ T lymphocytes specific for AFP, glypican 3 (GPC3), melanoma- associated gene 1, and New York oesophageal squamous cell carcinoma 1 (NY-ESO1).

These patient survival rates and tumor-specific T-cell responses are correlated25. On the other hand, genetic modifications brought on by hepatocarcinogenesis may result in amino acid alterations that ultimately result in the development of cancer neoantigens.

- **The immune cell microenvironment of HCC.**

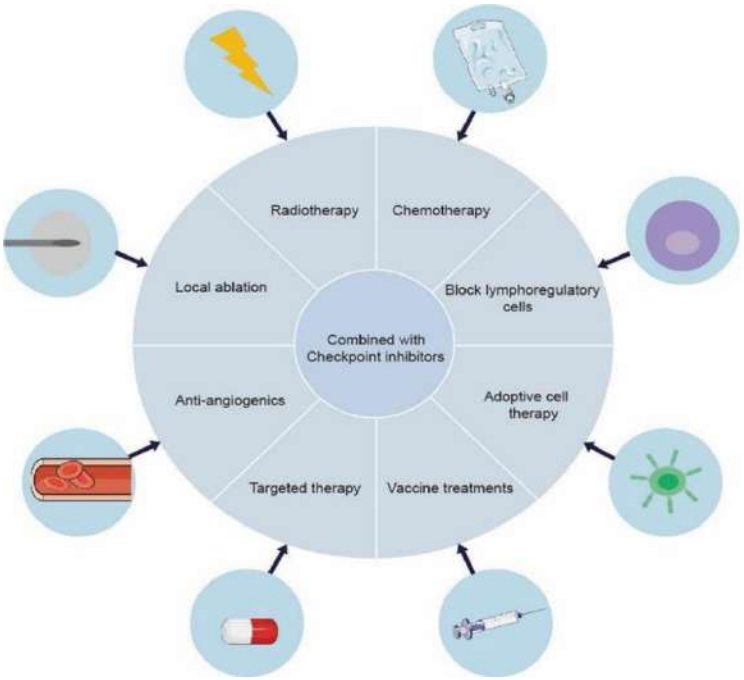
To promote tolerance to unfamiliar, innocuous substances like dietary antigens, the liver contains an anti-inflammatory immunological milieu. In humans, the maintenance of this tolerogenic environment involves collaboration between non-parenchymal resident liver cells like Kupffer cells, hepatic stellate cells (HSCs), and liver sinusoidal endothelial cells (LSECs). Kupffer cells, which reside in the liver, can function as antigenpresenting cells (APCs) in conjunction with LSECs and HSCs.

- **Immune checkpoint inhibitors in HCC**

Single agents. Individual agents.The PD1 inhibitor nivolumab was given accelerated approval in the USA for the treatment of patients with advanced HCC after sorafenib only four years after a pilot clinical trial demonstrated for the first time that CTLA4 blockade with tremelimumab can induce durable objective remission in patients with HCC and HCV infection. ICIs are used in every phase III research assessing systemic therapy in HCC

patients who have never received treatment. This condition is mostly a result of the dearth of efficient systemic therapy for HCC, given the relatively low proportion of patients who react to ICIs (ICIs) . Systemic treatments for HCC that are now being used in clinical practise or being developed rely heavily on PD1 and PDL1 inhibitors. Following the failure of sorafenib or intolerable toxicity, single-arm phase II trials using nivolumab and pembrolizumab have demonstrated unmistakable signals of action. additional immune checkpoint blockers.

Beyond PD1, PDL1, and CTLA4, there are more immune checkpoint molecules that can be targeted to activate an immune response against tumours. A worse prognosis in HCC is linked to high levels of PD1+ CD8+ T cells in the immune infiltrate105 and PDL1+ tumour cells113. While TIM3 expression on Treg cells results in increased suppressor activity, it is expressed on CD4+ and CD8+ TILs114 and TAMs115 from human HCC tumours and adversely influences T cell effector function116. Strong TIM3 expression and association with HCC cancers with reduced differentiation [13]



Diagnosis of Hepatocellular carcinoma

Blood tests to monitor liver function are among the procedures and tests used to identify hepatocellular cancer. imaging tests like MRI and CT. In some circumstances, a liver biopsy is performed to remove a sample of liver tissue for laboratory analysis.

Tissue Diagnosis of HCC

Up to 67% of new nodules smaller than 2 cm found during surveillance imaging in patients with cirrhosis are HCC, according to recent prospective

studies. Even though hepatic nodules between 1 and 2 cm in size have a 96% specificity rate for contrast-enhanced MRI, a considerable fraction of small HCC may appear hypovascular or have unusual characteristics, leading to a false-negative rate of 20%–38%.17 Finally, even with the best imaging methods, lesions with a diameter of less than 1 cm may be very challenging to characterise. A repeat USG exam should be performed after a lesion that is smaller than 1 cm in size after three months. Patients with chronic hepatitis B and cirrhosis, both fully developed and partially formed, may use these guidelines. The likelihood of HCC is substantially lower in all other patients who do not have cirrhosis, hence a biopsy should be performed for a certain diagnosis of HCC.The consensus statement from the Asian Oncology Summit from 2009 suggests that, in contrast to EASL and AASLD criteria, the characteristic features on contrast-enhanced CT or contrast-enhanced MRI are sufficient for the diagnosis of HCC, obviating the need for biopsy, for any nodule, regardless of size. When the diagnosis of HCC is made by diagnostic imaging (Level of evidence 1a, grade of recommendation A), a histologic diagnosis is not required. When a tissue type is revealed by imaging evidence, histologic diagnosis by biopsy is advised. :[15]

CONCLUSION :

Hepatocellular carcinoma is most common liver cancer. It is chronic liver disease and cirrhosis that are frequently present in advanced stages. Associate liver dysfunction with advanced tumour stages further curative therapy. Treatment options include liver transplantation or surgery to remove the malignant cells. HCC as well as other cancer can be prevented by appropriate measures such as HBV vaccination, universal screening of blood products and continues improment treatment in both surgical and nonsurgical approaches has beneficial to be survival.

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