IJBPAS, December, 2024, 13(12): 6347-6358

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

CURATIVE THERAPIES FOR HEPATOCELLULAR CARCINOMA

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Received 24th Sept. 2023; Revised 25th Oct. 2023; Accepted 7th March 2024; Available online 1st Dec. 2024

https://doi.org/10.31032/IJBPAS/2024/13.12.8512

ABSTRACT

Hepatocellular carcinoma (HCC) is a primary liver cancer that poses a substantial worldwide health challenge. It is frequently linked to underlying liver illnesses, most notably chronic liver inflammation and cirrhosis. Regular monitoring of high-risk individuals, such as those with chronic liver illnesses, is critical for early intervention and improved results. HCC is a critical illness for which early detection and treatment are critical. With its rising prevalence and frequent late-stage diagnosis, there is an urgent need for better curative therapy. Recent advances in systemic therapy, including as immune checkpoint inhibitors and tailored medicines, are showing promise in the treatment of HCC. Curative therapy for HCC have advanced tremendously, with a range of approaches customised to individual patient features and disease stages now available. On-going research into developing therapeutics holds the prospect of broadening the curative armamentarium for HCC, providing hope for enhanced survival and quality of life for those affected. This review provides in-depth look at curative approaches and new therapeutics for HCC.

Keywords: Hepatocellular Carcinoma, liver transplantation, Resection, Chemotherapy, Radiotherapy

1. INTRODUCTION:

1.1 Hepatocellular Carcinoma:

Hepatocellular carcinoma (HCC) is characterised as a liver-derived carcinoma that also involves a number of underlying conditions. An estimated 10.9 million new cases of cancer are reported globally year. With 749,000 new cases each year and 692,000 fatalities from cancer-related causes each year, liver cancer was found to be the sixth most common disease overall **[1, 2]**. East Asia, Melanesia, and sub-Saharan Africa have the greatest rates of HCC incidence, which account for 85% of all cases that have been documented worldwide **[3, 4]**.

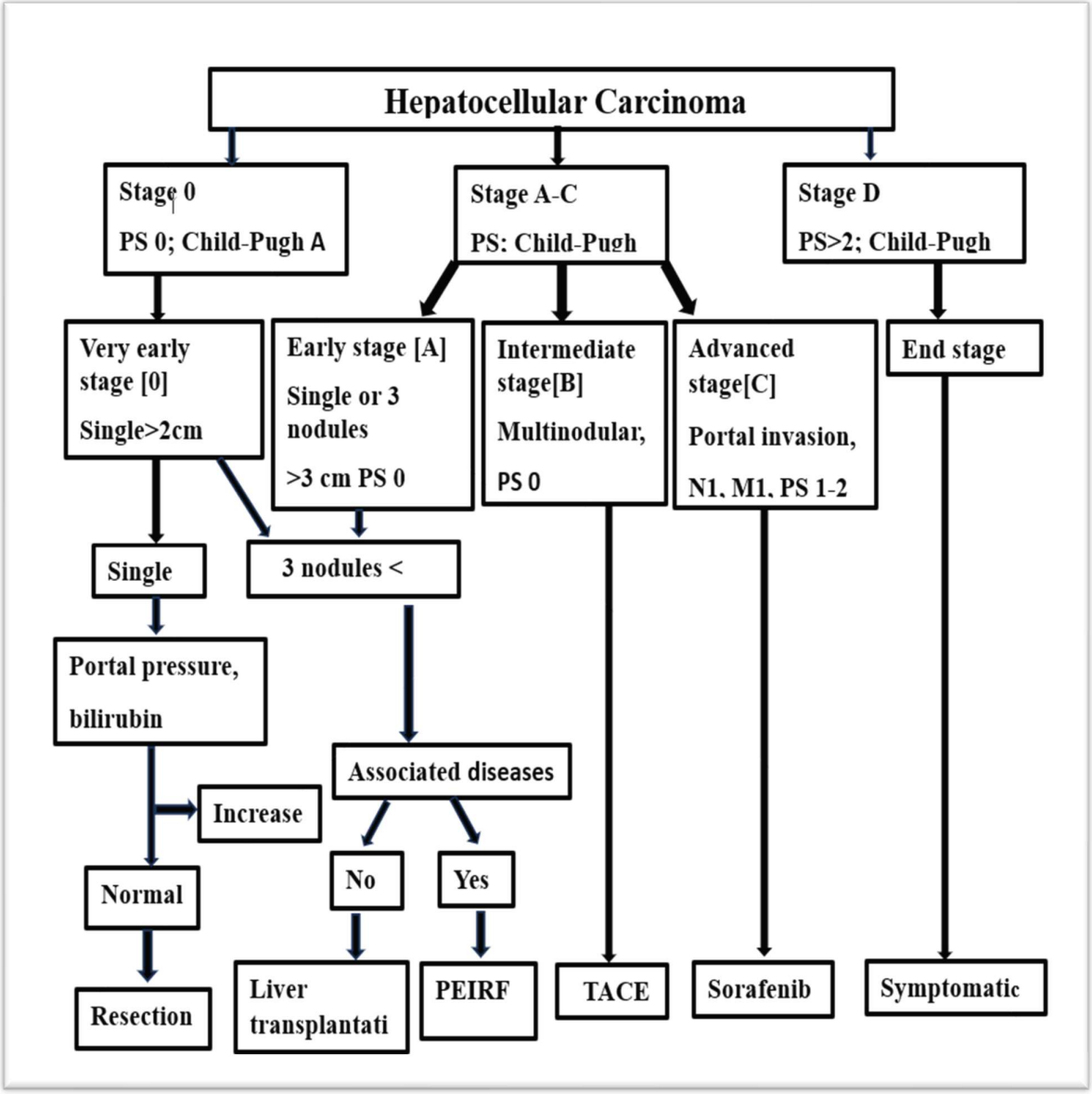

Figure 1: Stages of Patients with Hepatocellular Carcinoma

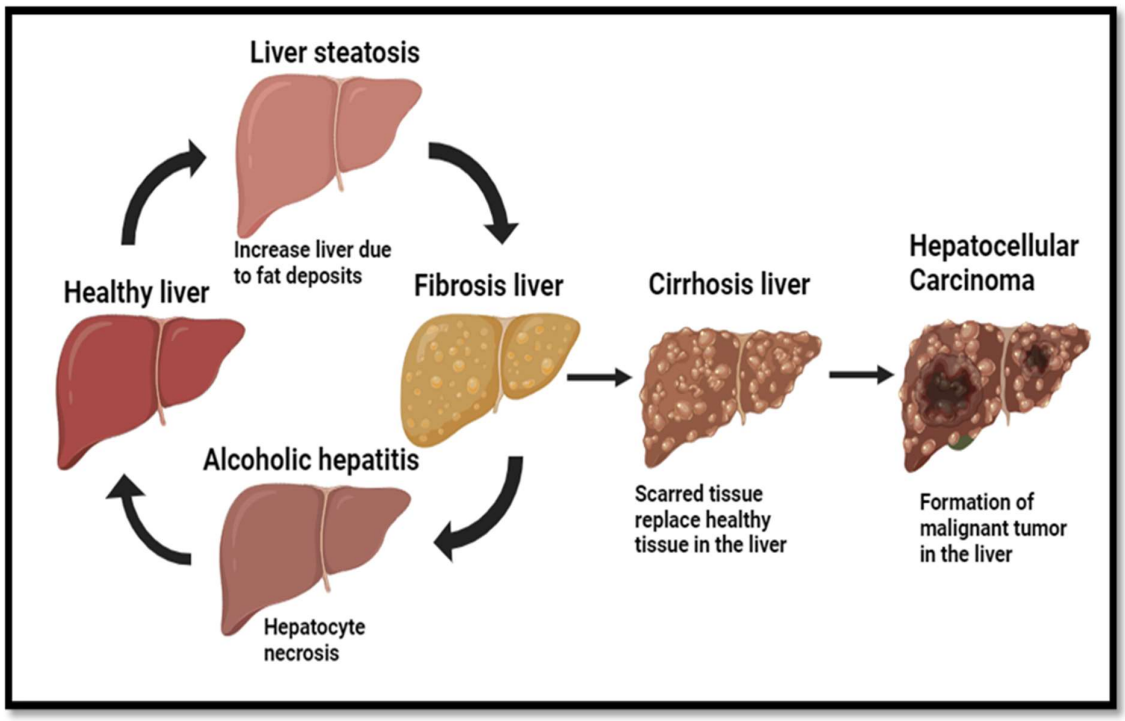

Figure 2: Stages of formation of Hepatocellular carcinoma

2. Current therapies for hepatocellular carcinoma:

2.1 Gene therapy:

Genetic modification is the technique of inserting therapeutic-grade RNA into an individual's cells to treat disorders with genetics. The delivery of the molecule might be done virally or non-virally, in-vivo or ex-vivo. In the context of cancer, the DNA coding for decreased tumour suppressive genes, small interfering RNAs that obstruct the replication of oncogenic mRNAs, or suicide genes that produce cells that cause cancer cells to undergo apoptosis can all be used to correct aberrant gene expression. To yet, just the ex vivo gene for cancer treatments formerly been granted FDA authorization, despite the fact that the FDA has approved in-vivo as well as ex-vivo gene therapy for a variety of disorders [5].

2.1.1. Gene Therapy Types:

a. Ex Vivo Gene Therapy:

The process of changing a cell's genetic composition outside of the body is known as ex vivo gene therapy. In the case of cancer, cells are taken from the patient, cultured, and modified in the lab so that they can kill cancer cells before being returned to the patient. The cells that are used the most frequently are known as CAR-T (chimeric antigen receptor-like T) cells. This technique changes the T-cells in the individual by use of a virus that produces the Chimeric Antigen Receptor (CAR) gene, which is the source of the phrase CAR-T cells. This receptor allows T lymphocytes to precisely attach to Cancerous cell without damaging

good cells. It is particular to cancer cells and varies depending on the kind of cancer.

b. In Vivo Gene Therapy:

DNA used in therapy are straight transferred into a patient body by a viral or non-viral delivery method in in vivo gene therapy. The method of administration may be an intravenous, intraarterial, intratumoral, intraportal, intrasplenic, or intrabiliary injection. Ex vivo gene therapy has proven to be more successful than in vivo gene therapy in treating cancer mostly due to its increased potential for unknown adverse impacts.

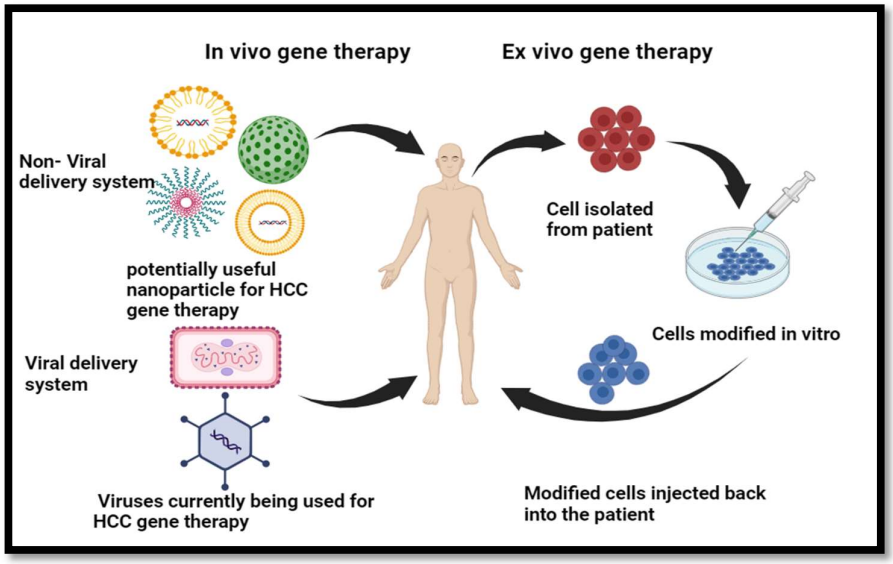

Figure 3: A summary of the many gene therapy methods utilised to treat HCC

2.2. Genome editing:

A post-transcriptional technique called "gene manipulation" allows genetic material from the genetic code to be changed. This process involves the majority of the enzymes in the adenosine deaminase reacting on RNA (ADAR) family. Reducing mRNA retention in the nucleus and changing fusion sites or coding areas are two ways that RNA editing might modify amino acids and impact translation **[6]**. The genetic variety of people and tissues is increased by variances in RNA editing **[7, 8]**. And its possible involvement in physiological cell processes may influence the onset of illness **[9, 10]**.

3. Prospects therapies for hepatocellular carcinoma:

There are several approaches to HCC treatment. The optimal course of action will be determined by the patient's liver function, overall functional status, and cancer stage. Curative therapy for HCC patients may involve surgical resection, LT, TACE, radiofrequency ablation (RFA), etc. These treatments may be successful in 20–40% of cases **[11, 12]**.

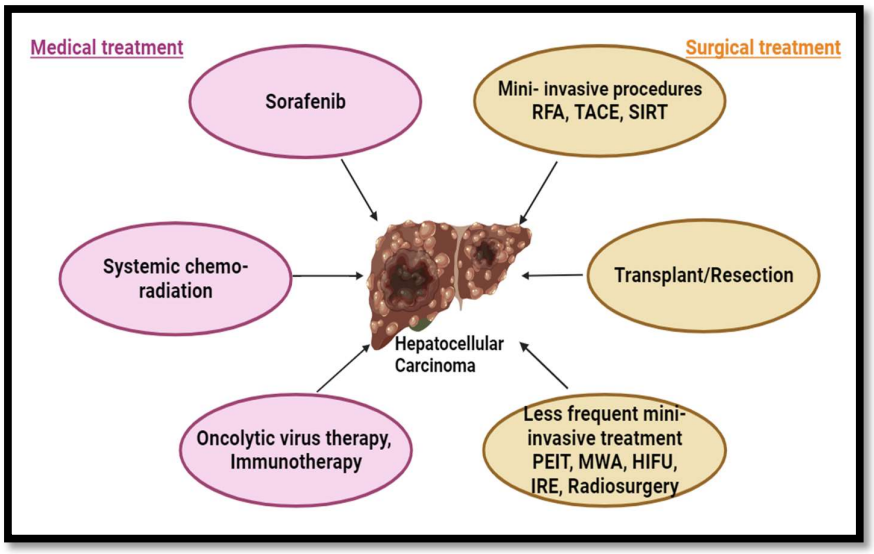

Figure 4: A list of the HCC treatments that are now available, both medicinal and surgical

3.1 Resection:

Surgical resection using a liver transplant or primary resection, is the therapy that has the best chance of curing HCC. The decision of the course of action to take is based on a number of considerations. For individuals without cirrhosis who have a single tumour without significant vascular invasion or extrahepatic dissemination, primary excision is the recommended course of action. Although LT has been demonstrated to be better to TACE or percutaneous ethanol injection (PEI), no randomised trials have been conducted to compare it with primary resection **[13]**.

3.2 Liver transplantation [LT]:

For individuals with pre-existing cirrhosis as well as applicants who are not fit for liver resection, LT is the most curative treatment. However, because to poor patient selection, disappointing findings, including significant recurrence rates and 5-year survival rates below 50%, have been noted.[14,15] Only individuals with early-stage HCC may typically undergo LT.

3.3 Living donor liver transplantation [LDLT]:

According to an analysis of the Adult-to-Adult Living Donor Liver Transplantation (A2LL) cohort, patients with HCC may be more likely to experience a recurrence after receiving living donor liver transplants (LDLT) as opposed to deceased donor liver transplants (DDLT). Compared to LDLT, DDLT requires a longer wait period, which may make it possible to identify physiologically aggressive tumours and remove those individual from the transplant waiting list.

3.4 Sorafenib:

Sorafenib was created in 1990 as a result of years of work on the creation of focused HCC therapies. Regardless of the severity of cirrhosis, sorafenib was

swiftly authorized by the Food and Drug Administration because to the lack of medical treatment options for HCC.[16] The oral multi-kinase inhibitor sorafenib significantly inhibits the serine/threonine kinase RAF, which stops cell proliferation. It has also been demonstrated to block the platelet-derived growth factor receptor and pro-angiogenic VEGF **17, 18]**.

3.5 Selective internal radiation therapy (SIRT):

In patients with HCC who are not qualified for conventional treatment, SIRT has more recently been established with relation to tumours greater than 7 cm in diameter, vascular invasion, and TACE failure. This method delivers radiation to the liver tumour by injecting microspheres that have been tagged with a radioisotope that produce b waves, like 90 Yttrium, to target HCC **[19]**. Numerous studies have recorded a range of responses, such as persistent sickness, full responses, and partial responses.

3.6 Percutaneous ablation:

For patients with BCLC 0-A tumours and early-stage HCC who cannot undergo LT or resection, percutaneous ablation is the recommended course of therapy. The two most regularly performed techniques are radiofrequency ablation and percutaneous ethanol injection. RFA has increasingly replaced PEI35 in use today since it requires fewer treatment sessions than PEI and has been demonstrated in several trials to have a higher complete necrosis rate as well as greater long-term survival rates.

3.7 Radiofrequency ablation [RFA]:

In 1990, the RFA was initially used, and in 2001, the FDA approved it **[20, 21]**. RFA is now the least intrusive therapy for advanced HCC that is used the most frequently. Rapid electromagnetic pulses are delivered by RFA, resulting in heat damage and tissue necrosis that is coagulative. Both the temperature reached and the heating period's duration affect the severity of the heat damage.

3.8 Percutaneous ethanol injection therapy (PEIT):

When an HCC patient with BCLC stage 0-A is not a good candidate for surgery, one of the most often used chemical ablation techniques is PEIT. Given its inexpensive cost and technological simplicity, it is still widely utilised. Alcohol is a cytotoxic substance that results in tumour necrosis, tumour microcirculation thrombosis, and the subsequent ischemia that follows **[22]**. Alcohol's harmful effect is successful because of the high the blood supply and the HCC's delicate consistency, which let alcohol to broadly enter through the tumour tissue. PEIT is typically employed in cases of minor HCC, where the rate of necrosis can drop to around 70% for cases above 2

cm but under 3 cm, and can reach 90–100% for cases under 2 cm **[23, 24]**.

3.9 Microwave ablation [MWA]:

HCC has also been treated using thermo-ablative techniques. Electromagnetic waves in the 1-300 GHz frequency range are the main component of MWA. Laparoscopically, percutaneously, and intraoperatively are just a few of the methods that can be used to carry it out. Compared to RFA, MWA has a number of benefits, including as the ability to focus on tissue at a higher temperature, a shorter treatment time, and a reduced risk of skin burns. Prior RCTs comparing RFA and MWA indicated that the two treatment modalities were equally effective; however, RFA was demonstrated to be marginally more successful than MWA in terms of local tumour management and to have a comparatively lower incidence of issues **[25]**.

3.10. Trans-arterial chemotherapy [TACE]:

For patients with stage B Barcelona Clinic Liver Cancer (BCLC) and intermediate HCC, TACE has been recommended as the initial course of therapy **[26, 27]**. TACE achieves its anticancer effect by causing blood flow embolization specifically targeted by HCC, ischemia, and necrosis of tissue by regional catheter-guided delivery of lipiodol-infused chemotherapy drugs **[28]**. Additionally, in an attempt to maintain liver transplant eligibility standards by stopping future tumour development, TACE is currently applied as a bridge treatment for HCC individuals waiting for liver transplantation **[29]**.

3.11. Highly-focused ultrasound [HIFU]:

Another non-invasive method for treating unresectable HCC is called high-intensity focused ultrasound (HIFU). This method uses mechanical energetic waves to target specific areas of HCC and then uses focused waves of heat to destroy tissue HIFU is a treatment for benign prostatic hypertrophy, uterine myomas and inoperable prostate cancer **[30-32]**. Furthermore, both animal and human research using HIFU have demonstrated its effectiveness in treating liver cancer **[33, 34]**.

3.12. Irreversible electroporation [IRE]:

The principal application of IRE was as an electro-chemotherapy to modify cell membrane permeability. The way that IRE works is by creating extremely brief electrical pulses that destabilise human cells and cause them to lose their membrane potential. This leads to the development of bigger holes in the cell membrane, which eventually induce cell death. IRE is currently widely utilised in water purification, sterilisation, or preprocessing; more recently, reports have indicated that it

may also be used to destroy tumour cells **[35-37]**.

3.13. Radiosurgery:

Leksell created the concept of radiosurgery in 1987 **[38]**. The upper spine and brain lesions were both treated with radiosurgery in this original model, now known as the Gamma Knife. More lately, computer-assisted radiosurgery procedure was created to allow treatment of additional organs, such as the liver **[39]**.

3.14. Oncolytic virus therapy:

The treatment of cancer using oncolytic viral therapy is a unique therapeutic method that has garnered considerable attention and research efforts recently. This therapeutic approach involves the use of a naturally occurring or genetically created virus that has the ability to destroy cancerous cells by inciting the defence mechanism, which as a result combats the malignant cells without endangering healthy organs **[40]**.

3.15. Immunotherapy:

The fight against cancers relies heavily on the immune system. Since it was first used in clinical settings, immunotherapy has completely changed how cancer is treated. For the cure of cancer, there are two checkpoint inhibitors available. The pathway related with programmed cell death protein 1 (PD-1/PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) **[41, 42]**.

CONCLUSION:

Finally, the integration of numerous curative therapies, as well as the discovery of novel agents and personalised medicine, holds great promise for furthering the field of hepatocellular carcinoma therapy. A multidisciplinary approach is required to optimise treatment techniques and enhance the overall prognosis for people dealing with this difficult cancer. Curative therapy for HCC look to have a bright future as research continues to yield new insights. Molecular profiling and personalised therapy strategies are becoming increasingly popular, allowing for more precise and targeted therapies.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation

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