Review Article

# HEPATOCELLULAR CARCINOMA: MANAGEMENT UPDATE

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## ABSTRACT

**Background:** Hepatocellular carcinoma (HCC) is one of the leading causes of cancer deaths worldwide. Cirrhosis and chronic hepatitis due to any cause are the main etiologic factors for the rising trend in Hepatocellular carcinoma globally. The recent advances in the field of medicine have shown promising perspective in the management of this disease.

**Aims and objectives:** The following preview will highlight the causes and diagnosis of hepatocelluar carcinoma. This discussion will also outline and discuss current updated approaches to patient care in clinical setting.

**Material and Methods:** A narrative literature review utilizing PubMed, Google Scholar and OVID as databases was carried out in September 2018. Keywords used were: "Hepatocellular carcinoma", "Management update in Hepatocellular carcinoma", "Workup of Hepatocellular carcinoma" and "Treatment modalities for Hepatocellular carcinoma". This literature search was confined only to studies performed on human beings and published in English language only.

**Keywords:** Hepatocellular carcinoma, treatment modalities of HCC, Radiological interventions for HCC.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is ranked as top 10 malignancies and holding 2nd position in list of cancer associated deaths around the world. Record shows that the incidence rate of HCC in developed states has almost risen to double during last 2 decades, largely due to cirrhosis and chronic hepatitis. Each year, more than 0.6 million deaths around the globe are attributed to HCC. HCC has the fastest growing death rate of any cancer in the United States and highly fatal or those who do not receive any liver-specific therapy.[1] Hepatitis B virus (HBV) infection is a main contributing factor along with family history of HCC as a synergistic phenomenon in African and most parts of Asian regions.[2]

Multidisciplinary team (MDT) is required for optimum management of HCC as there is frequent coexistence of chronic liver disease, variable biologic behavior of the tumor, wide heterogeneity in its presentation, recent advances in treatment modalities, with diverse responses to these therapies. However, rates of survival have improved in recent years through advances in interventional radiology and liver transplantation. In this narrative review, we outline the causes and diagnosis of HCC and discuss current updated approaches to patient care.

We as clinicians encounter patients with HCC on daily basis.

The following discussion will try to answer the following queries:

1. What is the common presentation of HCC?

2. What are the available treatment modalities for HCC?

3. How to manage HCC according to stage-wise involvement of liver?

## SEARCH STRATEGY AND RESULTS

To answer these questions, literature search was conducted using PubMed (MESH), Google scholar and OVID as search database engines. The following bolean terms were used in PubMed, Google Scholar and OVID searching:

1. Hepatocellular carcinoma and current treatment modalities

2. Hepatocellular carcinoma OR Carcinoma liver

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3. Hepatocellular carcinoma AND surgical interventions

4. Hepatocellular carcinoma AND radiological interventions

5. Hepatocellular carcinoma NOT metastatic carcinoma of the liver

Moreover, hand-searching was also conducted in libraries of College of Physicians and Surgeons Pakistan, Peshawar campus and Khyber Medical College, Peshawar. A limit of "Year 2000 till date" was applied on search databases. All these original papers/reviews/essays/guidelines were extracted and saved for review processing. Duplications were then subtracted and preliminary library of 35 results was made. The references of all these selected 35 articles were then individually searched by each author to find out high yield relevance accordingly. The significant articles published between 2005 to September 2018 were selected for this review. The high yield variables and information were extracted from these articles. The "QualSyst" checklist was utilized for bias assessment risk. This list is basically used as a standard operational tool in systemic reviews. All the important articles of last six years including Randomized controlled trials and systematic reviews/ meta-analysis were included in this review. Articles written in English language were included. Finally, a total of 10 articles, 7 belonging to PubMed, 1 from OVID and 2 from Google scholar were included.

### *Definition*

Malignant neoplasms of the liver parenchymal cells are defined as hepatocellular carcinomas.

### *Risk factors*

Known risk factors for HCC are cirrhosis, male gender, age older than 55 years (however, cases are reported increasingly in younger age groups), Asian and Hispanic ethnic groups, family history of HCC in first degree relatives, alcoholics (particularly obesity acts synergistically), tobacco use, diabetic patients, hypothyroid patients (especially females), obesity (especially in early adulthood), prolonged prothrombin time, thrombocytopenia and raised serum transferrin saturation. Literature is documenting higher risk of HCC in patients suffering from viral as compared to non-viral causes of cirrhosis and may be increased in persons with autoimmune diseases. Other associations are high viral loads of HBV replication, genotype C of HBV, co-infection with hepatitis D, patients of chronic hepatitis B having raised serum ALT levels, genotypes 1b and 3 of HCV, hemochromatosis (C282Y carrier state as a possibility), exposure to aflatoxin (TP53 gene mutation), alpha-1-antitrypsin deficiency, Porphyria cutanea tarda (PCT), tyrosinemia, Type 1 and type 3 glycogenesis, citrullinemia, orotic aciduria and radiation exposure. The concept of cirrhosis by itself as a predisposition for HCC or the underlying pathogenesis of cirrhosis as carcinogenic factors is still nebulous. In patients with the metabolic syndrome, it is thought that hepatocellular carcinoma may arise from hepatocellular adenoma even in the absence of cirrhosis. Uptil now, none of a study has provided any conclusive documentation for HCC association with long-term use of oral contraceptives(OC's). While sulfonylurea and insulin use may augment the risk of hepatocellular carcinoma, consumption of coffee, vegetables, white meat, fish, polyunsaturated fatty acids, aspirin use, statins and metformin use in diabetics appear to be protective.

### *Presentation*

In 80% of cases, HCC is associated with cirrhosis. Patient usually complains of cachexia, lethargy and weight loss. The rapid onset of hemorrhagic ascites mostly predilects hepatic or portal vein thrombosis by HCC or bleeding from a necrotic tumor. Approximately 3–12% of HCC patients complain bony pain while necropsies document histological bone metastases in only 20% of cases. Nonetheless, 20-25% of HCC patients can be asymptomatic. Fever is recorded in 10–50% of patients, as usually found in other malignancies. Hepatic veins invasion by HCC can cause Budd-Chiari syndrome and these patients present with tense ascites and tender hepatomegaly. Physical examination may show tender hepatomegaly, with occasionally a palpable mass. In Africa, a rapidly expanding abdominal mass in young patient is always investigated for HCC. There may be an audible bruit on auscultation over the tumor or a friction rub. This happens mainly when the tumor has already invaded surface of the liver.

HCC is associated with some paraneoplastic syndromes due to biochemical abnormalities usually without any clinical evidence. These paraneoplastic manifestations may be hypoglycemia (also manifested by end-stage liver disease), dysfibrinogenemia, hypercholesterolemia, erythrocytosis, carcinoid syndrome, hypercalcemia, raised thyroxin-binding globulin, porphyria cutanea tarda and alteration in secondary sexual characteristics like testicular atrophy, gynecomastia and precocious puberty. A large number of patients may have low platelets count in association with fibrosis or leucopenia. This may be the manifestation of portal hypertension and may not be due to infiltration of bone marrow by tumor, in contrast to other tumors. Furthermore, high percentage of HCC tumors can have either normal or high platelet counts just like ovarian and other GI malignancies, most probable due to raised levels of IL-6. It is estimated that 60–70% HCC in Pakistan is

attributable to Hepatitis C Virus. This is different from many other Asian Pacific countries where Hepatitis B Virus remains the predominant etiology.[3]

## INVESTIGATIONS

### *Serological assay*

Alfa fetoprotein (AFP) has got the status of being serum tumor marker for HCC; however, AFP levels are high in only up-to 70% of HCC patients. It must be kept in mind that chronic hepatitis also documents mild elevation of AFP levels (10-200 ng/mL [10-200 mcg/L] ). The more specific tests for HCC are lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) assay and des-γ-carboxyprothrombin (DCP). This DCP protein is raised in 90% of HCC patients but may also be elevated in vitamin K deficiency states and even in patients on warfarin therapy. It is also a predictor of portal vein invasion. Both these proteins (AFP-L3 and DCP) are FDA approved. As a routine it is recommended that all patients presenting with either recent onset hepatic mass or other parameters of new-onset hepatic decompensation should begin with standard liver function tests, including PT, aPTT, serum albumin, serum transaminases, γ-glutamyltranspeptidase and alkaline phosphatase levels. Then AFP, vitamin B12, ferritin, AFP-L3, DCP levels and antimitochondrial antibody should also be considered. However AFP-L3 and DCP are not yet available in Pakistan.[2-5]

## IMAGING

### *Ultrasound of liver*

An ultrasound (U/S) for liver is the best imaging tool for screening. Asian oncology summit recommeds 3-6 monthly U/S plus AFP for screening in cirrhotic patients. Although U/S has sensitivity and specificity of >90% in detecting HCC, its efficiency is compromised in liver cirrhosis. Its yield largely depends on expertise of sinologist. [3]

Both American and European Guidelines consider biopsy or advanced imaging techniques, for nodules > 1 cm, detected on ultrasound. Until now, no outcome studies have been performed to show that survival is prolonged by a biopsy of indeterminate nodules > 1 cm rather than meticulous follow-up for growth.[1,6]

Majority of patients in Pakistan's perspectives having risk factors for HCC do not undergo screening. Unfortunately, we do not have nationally accepted guidelines for screening high risk patients and physicians at large have a variable practice in terms of choice of investigations and time period between them. The most common trend is 6 monthly U/S and serum AFP level .Many time, screening U/S is performed by inexperienced sonographers. Background cirrhosis makes interpretation of U/S findings difficult. Less than 10% patients are diagnosed with HCC on screening in Pakistan and that perhaps explains the delayed presentation and poor prognosis in majority of HCC patients.[7]

Triphasic CT Vs Contrast enhanced MRI abdomen HCC can reliably be diagnosed on imaging report without confirmatory biopsy. [6] Multiphasic helical CT and MRI are the highly recommended imaging studies for identifying the tumor site and its vascularity. The use of gadoxetic acid in MRI further enhances its sensitivity. Tiny lesions of less than 1 cm are normally difficult to characterize. HCC is typically characterized by Arterial phase enhancement followed by delayed venous washout.[6]

AASLD supports both multiphasic CT or multiphasic MRI for the HCC diagnostic evaluation.6 With regard to overall accuracy, several studies compared multiphasic MRI using an extracellular agent versus multiphasic CT. MRI with an extracellular agent provided higher pooled sensitivity than CT with similar specificity. Although multiphasic MRI may be marginally more sensitive than CT in a pooled analysis of comparative studies, the differences in pooled diagnostic performance are insufficient to recommend MRI over CT. In contrast to multiphasic CT, multiphasic MRI has several advantages and disadvantages. Advantages include greater soft tissue contrast, more comprehensive assessment of nodule and background liver tissue properties, and absence of ionizing radiation. Disadvantages include greater technical complexity, longer scan times, lower throughput, increased susceptibility to artifact, less consistent image quality (largely because of patient factors such as breath holding, difficulty holding still, or high volume ascites), larger number of potential contraindications, higher charges, and especially outside the United States—lower availability and longer scheduling backlogs. From a patient perspective, CT is faster, more spacious, and provokes less claustrophobia, but it exposes patients to radiation. Both modalities require IV access and contrast agents, the use of which may be problematic in patients with acute kidney injury or chronic renal failure.[6]

### *Liver Biopsy*

Routine use of liver biopsy is not suggested, but can be considered in selected cases, like those in which diagnosis is required to affect therapeutic decision making .However, biopsy has an increased tendency of bleeding, and tumor seeding, although 2% and the possibility that a negative biopsy is due to the failure to obtain tissue representative of the nodule rather than a truly benign nodule.[2,6]

Serste et al done a study on 74 patients with liver nodules identified by surveillance ultrasound, to determine best diagnostic approach among CT, MRI and biopsy for HCC. The authors concluded that sensitivity and specificity of the combination of the two diagnostic tests was 98% and 81%, respectively, and that biopsy could be reserved for those without definitive findings on either CT or MRI.[6] Biopsy helps to distinguish between primary HCC, adenocarcinoma or secondaries. Laparoscopic approaches can also be used. For suspected cases of portal vein involvement, a core biopsy of the portal vein may be performed safely. If positive, this is regarded as an exclusion criterion for transplantation for HCC.[5] Core liver biopsy of the liver mass histologically proves the presence of HCC. Bleeding tendency is more compared to other malignancies, because (i) the tumor is highly vascularized (ii) patients often have low platelets, and liver-dependent clotting factors. Ascites also raise hemorrhagic tendency.[5] Liver biopsy is though diagnostic, but has risk of seeding along the needle tract in (1-3%). Guidelines with some differences usually recommend 3 monthly ultrasound for lesions upto 1cm, followed by further investigation of enlarging lesions. For lesions 1 cm or larger, biopsy can be deferred when characteristic arterial hypervascularity and delayed washout are demonstrated on either multiphasic helical CT or MRI with contrast enhancement (or both) or if surgical resection is planned.[2] Liver biopsy is advisable in lesions without cirrhosis to exclude metastatic tumor.

### *Treatment Modalities*

HCC has a poor prognosis even in developed countries and 5-year survival is only 10%. Survival is even worse in developing countries and mortality is roughly equivalent to incidence rates.[8] International Agency for Research on Cancer (IARC), presented their statistics in 2015, that showed the mortality to incidence ratio for HCC is 0.95 and geographical patterns of incidence to mortality are nearly uniform.[9] Early detection of HCC is critical in ensuring optimal treatment. Tumor characteristics including its size, multinodularity and vascular involvement, underlying liver function assessed by Child-Pugh score and performance status (Eastern Cooperative Oncology Group performance status) play an imperative role in survival.

The natural history of HCC is inconstant. Cases of advanced tumors (vascular invasion, symptoms, extra-hepatic spread) at time of presentation have a median survival of 4 months, even with or without treatment. Literature is not helpful in interpreting the treatment results. It would be unjustifiable to consider survival as a measure of efficacy of different treatment modalities, because of the adverse effects due to underlying liver disease. Key of comprehensive management of HCC patients is the team work of hepatologist, interventional radiologist, surgical oncologist, resection surgeon, transplant surgeon, and medical oncologist.[5]

The Barcelona-Clinic Liver Cancer (BCLC) staging system has got status of being the most reliable guideline to decide treatment options and has been recognized by many guidelines including AASLD, EASL-EORTC and ESMO-ESDO [with two modifications: (i) Portal hypertension is omitted from the algorithm and gives more freedom in the clinical decision for resection. (ii) Patients with poor liver function (Child-Pugh C) and tumor extent within the Milan criteria should, in our opinion, not be deprived of the possibility of liver transplantation and are therefore not classified as terminal stage].[1]

### *Stage 0/V-Early Stage*

Doubling time of very early lesions can be upto 10–20 months or they might persist quiescent for a significant period of time. In this setting, resection and ablation have reached tremendous survival outcomes of almost 60–70% at 5 years.[10]

### *Surgical Resection*

As a general concept, resection is considered to be the first option for local lesions in non-cirrhotic liver. According to the guidelines ratifying BCLC staging system, appropriate candidates for a resection are non-cirrhotic patients; as in cirrhotics any major liver surgery can lead to liver failure, and lesion should be single <2 cm, with normal portal pressure , at score zero of Performance status i-e patient is Fully active, able to carry on all pre-disease performance without restriction. In contrast, JSH and KLCSG-NCC states that surgical resection can be performed in patients with ≤ 3 intra-hepatic tumors without macro-vascular invasion in a fully functioning liver.[1] hence it is only for child A. For safer resection it is better to occlude portal vein preoperatively, to cause atrophy of the affected lobe leading to compensatory hypertrophy of the noninvolved liver. At least 2 cm tumor free margin is recommended, after resection for a better survival outcome than, provided sufficient remnant liver volume is maintained. For non-cirrhotics, recommended minimal critical remnant liver volume for resection is approximately 25% (15–40%) and 50% (25–90%) for cirrhotic livers. Studies showed post-resection 5-year survival rates of 41-74% in single liver tumors without cirrhosis.[12, 13]

### *Stage A/Early Stage*

Local ablation (thermal, radiofrequency [RFA], or

microwave ablation (MWA]), and local injection therapies), are effective options recommended for early stage lesions. As malignant lesions are commonly associated with cirrhosis, therefore possibly they will not tolerate major surgical loss of hepatic parenchyma and they would be eligible for orthotropic liver transplant (OLTX).

## LOCAL ABLATIVE THERAPIES

### *This includes*

Radiofrequency ablation (RFA)

Microwave ablation (MWA)

Cryosurgery

Percutaneous ethanol injection (PEI)

Local ablation therapy is considered to be a second option after resection for patients with a solitary tumor or up to 3 tumors ≤ 3 cm each and good hepatic function (Child-Pugh A/B).[1]

Radiofrequency Ablation (RFA)

Radiofrequency ablation (RFA) is considered 1st option for ablation.[11] Ethanol injection is not much effective in locally controlling the tumor, but when the residual viable tissue is minimal, it can better provide complete response.[12] FRA and PEI are both equally effective in single lesion of ≤ 2 cm. RFA uses high temperature of upto 80-100 -C to ablate tumors. It can destroy a tissue upto 7 cm zone in which probe is applied, therefore would be adequate for a tumor size of 3-4 cm. The heat reliably kills cells in its zone. There is a risk of bile duct injury and obstruction, while using RFA for lesions closed to portal pedicle. This limits the location of tumors that are anatomically suited for this technique. CT or ultrasound guided RFA is more accurate than using probe blindly. As tumor size increases, especially ≥ 5 cm, the effectiveness of RFA-induced necrosis diminishes. For such cases, prospective randomized trials have shown better results in using combination of TACE and RFA, than using any of them alone.[5] For tumors that are 3.1-4 cm in diameter, Cryoablation may result in slower tumor progression than radiofrequency ablation.[2]

### *Microwave Ablation*

Microwave ablation (MWA) is alternative active thermal ablation method which provides continuous and uniform ablation with electromagnetic waves at frequencies more than 900 kHz.[12] MWA provides larger necrotic zones, thus leading to higher rates of tumor destruction. MWA is consider to be superior to RFA as it overcomes the "heat-sink" effect which is due to cooler blood flowing in vessels proximal to the tumor that causes incomplete ablation.[13] MW is technically easier than RFA, as well.[14]

### *Percutaneous Ethanol Injection (PEI)*

Several studies have recommended PEI as method of local ablation, and is in use for the last many years. The high incidence of local recurrence (33–43%) has limited its use now.[13] in this technique multiple injections (average three),of ethanol are given directly into hepatic artery feeding the tumor. The maximum size of tumor reliably treated is 3 cm, even with multiple injections.[5] Almost 1-2 sessions/week are done until tumor gets fully necrosed. Then post-procedure imaging is done after 1 month and then 4 monthly thereafter. While comparing the two, in a recent meta-analysis, it is concluded that survival rates with RFA are better than those treated with PEI.[15]

### *Cyberknife Robotic*

Advanced robotic radiosurgery system, uses cyberknife technique for ablating benign tumors, malignant tumors and other medical conditions. It's a method of delivering radiotherapy with the intention of direct and accurate targeting than standard radiotherapy.[3] The two main elements of the Cyber Knife are: Radiation produced from a small linear particle accelerator (Linac) A robotic arm which allows the energy to be directed at any part of the body from any direction The Cyber Knife System is routinely used to treat liver cancers with a procedure called stereotactic body radiation therapy (SBRT). SBRT accurately delivers the radiations to target, with an advantage of sparing healthy liver tissue and nearby organs from harmful exposure. Synchrony® Respiratory Tracking System, works in conjunction with cyber knife that enables the patient to breathe normally during their treatment sessions, and radiation beam tracks movement of tumor during real time. As a result, the Cyber Knife is a much comfortable for the patients, with accurate delivery of radiations requiring only one to five sessions.[15] This modality is now available in Pakistan as well.

### *Liver Transplant (LT)*

In cirrhotic patients with HCC at TNM stage 1,2 best option is OLTX which increases survival to almost that for non-cancer cases.[5]

Main inclusion criteria for LTx, to identify the most appropriate paients, is Milan's criteria. Transplant is recommended for the patients with single lesion not larger than 5 cm, or up to three lesions with each less than or equal 3 cm. Early stage HCC, undergoing LTx in specialized liver transplantation centers, has 5-year overall survival rate upto 75% with a risk of recurrence less than 15%. Several studies report peri-operative mortality and 1 year mortality to be approximately 3 and ≤ 10%, respectively.[13] Milan's criteria was expanded

after several studies, to the University of California San Francisco (UCSF) criteria for LTx for HCC (one tumor ≤ 6.5 cm or up to three nodules with the largest ≤ 4.5 cm, and the total tumor diameter ≤ 8 cm). These criteria have an overall survival comparable to those within Milan criteria, both prospectively and reterospectively.[16] Thus for liver transplant, patient could be in Child class A/B/C, with either in Milan's criteria, or expanded criteria, with AFP levels <1000ng/ml and no gross vascular invasion. Prospective studies showed exceptionally high post- OLTX recurrence rates in patients with AFP levels >1000 ng/mL.[5]The standard method to prioritrize cirrhotic patients to the LTx waiting list, is MELD score, though it was previously used as a mortality predictor in cirrhotics. Later, to increase percentage of LTx performed for HCC, a "MELD exception" has been developed to assign additional points to the HCC patients on the basis of the tumor burden this has increased the percentage of LTx , upto 30-40% performed for HCC. [13]

HCC may progress while waiting for an organ and this impairs the intention to treat and patient may drop out from waiting list.[10] To control this progression, concept of bridging was introduced. Bridging is actually a pre-transplant treatment that allows patients to stay on the waiting list longer, giving them better opportunities to be transplanted, by down staging ,stabilizing their tumor and preventing further growth. Resection, ablation, trans-arterial embolisation and trans-arterial radiation or sorafenib are commonly used to bridge patients to transplant. Liver transplant is suggested as a preliminary option in decompansated cirrhosis.[1] Studies revealed that HCC patients with baseline serum level of AFP >200 ng/mL exhibit significantly worse outcomes, when on waitning list. Although steady increase of AFP >15 ng/mL/month,is considered to be much worse determinant.[17] Therefore, AFP levels of 300, 400 and 1000 ng/mL are considered as delisting indicators.[18-21] Still, these statistical calculations are difficult to apply to an individual patient. A healthy person can donate his 50% liver. TACE is the most common method used for down-staging, followed by radiofrequency ablation (RFA), radio-embolisation and surgical resection. Most programmes have concluded Milan's criteria as the endpoint of down-staging to be conserved for at least 3–6 months.[22]

### *Stage B/Intermediate Stage*

## TRANSARTERIAL THERAPIES

Five varieties of Trans arterial therapies are currently available, including Trans arterial Chemoembolization (TACE), Trans arterial embolization (TAE), trans arterial bland embolization, trans arterial chemotherapy and trans arterial radio embolization (TARE).

### *Transarterial chemoembolization (tace)*

TACE is positioned as the first-line option for BCLC B patients, according to Cumulative meta-analysis of the informative trials [23] .patients with large multifocal lesions or unresectable cases but compensated liver function, without evidence of vascular invasion or extra hepatic spread, TACE is standard treatment modality available for them.[13] For TACE, a substance is required that is selectively retained within the tumor and increases chemotherapy exposure to the affected hepatic lobe, e.g. doxorubicin suspended in lipiodol is injected into hepatic artery, following this procedure, blood supply to tumor is blocked via polyvinyl alcohol beads, starch micro-spheres, metallic coils, or autologous blood clots, using angiographic catheter. Drug-eluting beads that obstruct arterial vessels and sustained release chemotherapy, improves drug delivery ,and minimum systemic chemotherapy hence increasing tolerance to TACE. Loss of vascularity on CT without size change may be an index of loss of viability and thus of response to TACE.[24,25] Studies showed that for lesions >3cm, combination of TACE and RFA is superior to any of them alone.[26,27]

### *Transarterial radioembolization (tare)*

Selective internal radiation therapy (SIRT) is considered as a well tolerated therapeutic option for intermediate-stage HCC.[28] In contrast to TACE, TARE lodge yttrium-loaded glass or resin spheres in feeding vessels and performing its major task through local action of beta radiations . The few cohort studies with heterogeneous populations suggest that it may provide similar survival rates to TACE and sorafenib chiefly in the setting of portal vein thrombosis (PVT).[10,29] Radioactive element, in radio embolization widely used is yttrium 90. The stable element zirconium-90 with a half-life of 2.67 days (64.2 h), is derived from he beta decay of yttrium 90. It has highly cytotoxic emitting electron, that directly destroy the target tumor. Tissue penetration of Y90 ranges from 2.5 to 11 mm. A radiation dose of up to 170 Gy can be administered.

Patients with un-resectable HCC ,in intermediate stage either child A,B, with multi nodular lesion, and a life expectancy of at least 3 months are considered eligible candidates for TARE; but cases with excessive tumor burden and limited hepatic function are in-eligible . Adverse effects with TARE include nausea, abdominal pain, gastrointestinal ulcers, and fatigue. TARE is a primarily outpatient procedure, in comparison to TACE.[30]

### *Stage C/Advanced Stage*

## SYSTEMIC CHEMOTHERAPY

Systemic chemotherapy gives unfavorable results. HCC is one of the most chemo-resistant tumors; and is poorly tolerated by cirrhotic due to adverse side effects. Hence guideline do not recommend systemic chemotherapy in advanced tumors.[31]

### *Molecular Targeted Therapy*

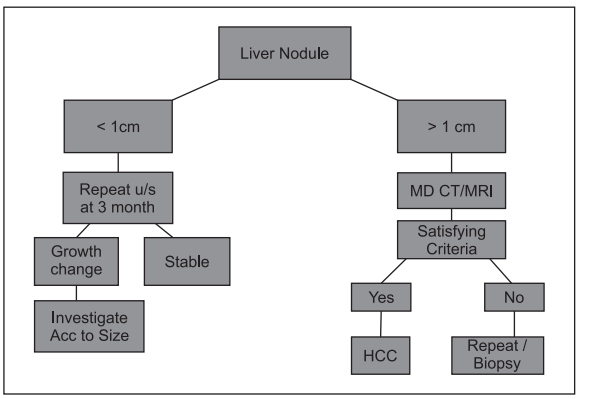
Hepato-carcinogenesis is associated with epigenetic and genetic alterations that eventually lead to an alteration in the molecular pathways resulting in uncontrolled growth of the hepatocytes.[32,33] For patients with preserved liver functions and unrespectable HCC, which is not suitable for percutaneous ablation or TACE, AASLD recommends sorafenib as a first line therapy in these cases. [1] It targets both the Rafmitogenic pathway and the vascular endothelial growth factor receptor (VEGFR) endothelial vasculogenesis pathway. However, tumor responses were negligible and the survival in the treatment arm in Asians was less than the placebo arm in the Western trial.[5] The Sorafenib HCC Assessment Randomized Protocol (SHARP) phase III trial of sorafenib versus placebo for un-resectable HCC showed that survival could be significantly enhanced in the treatment arm with only 2% of the patients having tumor response but 70% of patients having disease stabilization.[5] To define a relative role of TARE in relation to sorafenib, randomized studies are going on. The idea of utilizing TARE is now expanding with advancements of interventional oncology.[34]

Since long, Portal vein thrombosis was considered to be relative contraindication for trans-arterial chemoembolization (TACE) in hepatocellular carcinoma but now, several studies including a meta-analysis revealed that cases of unresectable HCC with portal vein thrombosis, treated with TACE, have better overall survival rate. According to a study by Luo L Cases of unresectable HCC plus portal vein thrombosis, treated with TACE using cisplatin and iodized oil showed a significant survival rate. 2.[31] However larger sample size is recommended for a prospective study to establish the potential of TACE in treating HCC complicated with PV thrombosis.[31,35] General population though better tolerate Sorafenib, but still some experience mild toxic effects, including diarrhea, fatigue, weight loss, rash, or superficial skin desquamation and hand-foot skin reaction, hair loss, anorexia, nausea and abdominal pain. The main attractiveness of 90 Yttrium therapy in advanced HCC is its safety in the presence of major branch portal vein thrombosis, where TACE is generally not recommended. Furthermore, external-beam radiation has been reported to be safe and useful in the control of major branch portal or hepatic vein invasion (thrombosis) by tumors.

## PROGNOSIS

Long-term survival is associated with resection or ablation or transplantation, all of which can yield >70% 5-year survival.

Untreated patients, with multinodular tumor, without vascular invasion, are having median survival of approx 16 months. TACE improves median survival up to 20 months. Serum AFP>200, or >15 ng/ml/month rise predicts worse outcome. Advanced tumors are having median survival is 6 months.




AASLD Guidelines recommendation for HCC screening in high risk cases 4

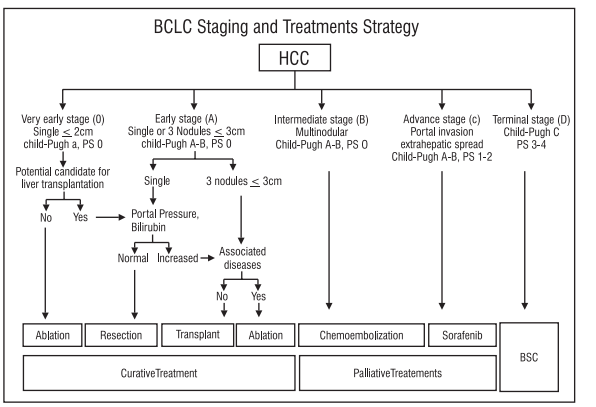
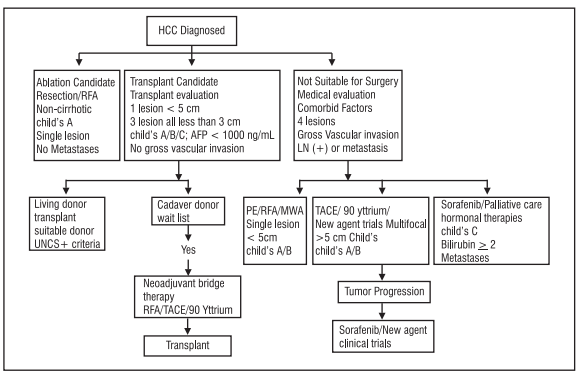



Fig 1: Barcelona clinic liver cancer (BCLC) standing classification and treatment schedule, Patients with very early hepatocellular carcinoma (HCC) (Stage 0) are optimal candidate for resection. Patients with early HCC (Stage A) are candidates for radical therapy (resection, HCC (Stage B) benefit from transcatheter arterial chemoembolzation (TACE). Patients with advanced HCC, defined as presence of macroscopic cascular invasion, extrahepatic spread, or cance-related symptoms (Eastern Cooperative Oncology Group performance status 1 or 2) (Stage C), benefit from sorafenib. Patients with end-stage disease (stage D) will receive symptomatic treatment strategy will transition from one stage to another on treatment

failure or contraindications for the proceudure. CLT, cadaveric liver transplantation; LDLT, living donor liver transplantation; PST, Performance status Test. (Modified from JM liovet et al: JNCI 100:698, 2008)




Hepatocellular carcinoma (HCC) Treatment algorithm. The initial clinical evaluation is aimed at assessing the extent of the tumor and the underlying functional compromise of the liver by cirrhosis. Patients are classified as have resectable disease or unresectable disease or as being candidates for transplantation. AFP, a fetoprotein; LN, lymph node; MWA, microwave ablation; OLTX, orthotropic liver transplantation; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; UNOS, United Network for Organ Sharing. Child's A/B/C refers the Child-Pugh classification of liver failure

## CONCLUSION

HCC is one among the top most deadly malignancies, worldwide. Advances in the understanding of disease process have improved screening and surveillance programs, the main target being early detection and treatment of HCC. Current guidelines in general are similar, with some inconsistencies in surveillance and treatment recommendations because of regional differences in disease and available resources ,for management., this makes it un-feasible to have a universally accepted guideline for all HCC patients around the world. Recommendations from the 3 groups (Asia, Europe, and USA) are influenced by geographic differences in the prevalence and biology of the disease (i.e., areas of increased hepatitis B prevalence) and available assets (organ availability for LT, finances, and accessibility to treatment). It is important to consider these deliberations when treating patients with HCC, and formatting its management guidelines. Thus to summarize treatment of HCC, we can recommend: STAGE 0,HCC <2 cm: RFA, PEI, or resection. Single HCC 2-3cm: RFA/MWA/PEI. HCC >3cm: combination of RFA with TACE. Stage A (Milan's criteria, expanded criteria) or stage O not suitable for resection needs OTLX.

Stage B, multifocal, compensated cirrhosis without portal vein invasion: TACE is indicated, if portal vein is involved, better to choose TARE instead. OR Multiple uni-lobar tumors or tumor with vascular invasion: TACE or sorafenib. Bi-lobar tumors, no vascular invasion: TACE with OLTX for patients with tumor response. Extra-hepatic HCC or elevated bilirubin: Sorafenib or bevacizumab plus erlotinib (combination agent trials are in progress).

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Following authors have made substantial contributions to the manuscript as under:

**Haider I:** Main idea, Literature review, overall supervision.

**Amin B:** Data analysis, article writing and formatting.

**Badshah A:** Literature Search, final draft, proof reading.

**Raza A:** Data compilation, proof reading.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.