Review Article

Malignant Transformation of Cirrhotic Liver

Adekanle O[1], Oje MM[2], Ndububa DA[1]

[1]Department of Medicine, Faculty of Clinical Sciences, Obafemi Awolowo University, [2]Department of Medicine, Obafemi Awolowo University Teaching Hospitals, Ile-Ife, Osun State, Nigeria

ABSTRACT

Liver cirrhosis (LC) is a disease of the liver characterised by replacement of the normal liver architecture by nodules. It is a disease that is commonly diagnosed at a late stage in Nigeria. Chronic hepatitis B infection is the most common cause of LC in Nigeria, probably followed by chronic hepatitis C virus (HCV) infection and alcohol consumption. LC often transforms to hepatocellular carcinoma (HCC) and this may be diagnosed for the first time at presentation. In fact, most HCC in Nigeria occur on a background of LC in up to 80% of cases. Few cases of LC that are therefore diagnosed at an early stage will need good clinical and laboratory assessment and skilled management to mitigate early transformation to HCC. The pathogenesis and pathogenetic pathways LC transforms to HCC as well as the roles chronic hepatitis B virus and HCV play in the transformation are highlighted. In addition, the detection of early onset of HCC in the cirrhotic liver and the challenges of investigation modalities and treatment are the highlights of this review article.

Key words: Hepatocellular carcinoma, liver cirrhosis, malignant change

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INTRODUCTION

Liver cirrhosis (LC) is a pathologic entity defined as diffuse hepatic fibrosis with replacement of the normal liver architecture by nodules.[1] LC is the final common pathway for many types of chronic liver disease. When liver injury occurs, its progression to LC may take weeks to years. The progression of LC to malignancy on the other hand varies in clinical presentation. In areas such as Europe and North America, where the incidence of hepatocellular carcinoma (HCC) is low, majority of patients develop HCC that is asymptomatic on a background of micronodular LC resulting from long years of alcohol consumption or in patients diagnosed with the metabolic syndrome.[2] In areas of high incidence of HCC like the southeast Asia and sub-Saharan Africa, chronic hepatitis B (CHB) infection is the major cause of LC and the liver nodules are usually macronodular.[3] LC is a limiting factor for anticancer therapy in cirrhotic liver with a cancerous growth.[4] This review is therefore focused on the development of HCC in LC, factors associated with its occurrence, the influence of chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV) and the challenges of management.

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EPIDEMIOLOGY

LC is a major cause of death; it ranks as the14th most common cause of death worldwide and 1.2% of all deaths in the United States of America.[5] HCC on the other hand is the fourth most common cancer and the second most common cause of cancer deaths in the world.[6] In Nigeria, there are no accurate data on the incidence of LC, neither the incidence of HCC in LC. However, liver disease admission in Nigeria ranges between 6.3% and 7.9% of all medical admissions of which HCC is the most common followed by LC in a ratio of approximately 2:1.[7,8] Several studies on LC showed that patients usually present at a late stage in Child-Turcotte-Pugh (CTP) Class C,[9] with the age incidence in the early forties to the sixties,[10-12] while patients with HCC usually present in their mid-forties, with age range of between 40 and 60 years.[13,14] In addition, many cases of HCC occur on a background of LC in close to 80% of cases.[13,14] Notably, HCC is a male-dominant disease, and the incidence of the disease is approximately three to four times higher in males than in females.[6,14] HBV infection is associated with higher

Address for correspondence: Dr. Adekanle O, Department of Medicine, Faculty of Clinical Sciences, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria.
E-Mail: olusegunadekanle@yahoo.co.uk

incidence of HCC in persons with LC occurring in high endemic areas of the world as well as in those from western countries.[6]

PATHOGENESIS OF MALIGNANT TRANSFORMATION IN CIRRHOTIC LIVER

Histologically, the fibrosis of LC occurs with deposition of extracellular matrix proteins and collagen in higher-order structures within the liver parenchyma. Hepatic stellate cells and fibroblasts happen to be the major producers of collagen.[15] Hepatocellular cancer occurs at an average rate of 2.3% per year in HBV induced LC from one report in Japan.[6] The risk factors for the occurrence of HCC in LC are: The type and severity of the LC, male sex factor, patient who are older, presence of comorbidities, very high serum HBV-DNA levels and significant alcohol intake. Lin *et al*.[16] followed up 39 patients with LC and 44 pathologically confirmed cirrhotic nodules, 14 of the nodules had developed HCC within a median follow-up of 26.7 months. There are HBV-related factors that induce the transformation of LC to HCC which include high levels of serum HBV-DNA and hepatitis B surface antigen (HBsAg), patients with HBV genotype C, HBV infection with hepatitis B e antigen positivity and HBV infection with mutation in the basal core-promoter gene. The non-viral factors that induce the occurrence of HCC in LC are; older age, male gender and high serum levels of both alanine aminotransferase (ALT) and alpha-fetoprotein (AFP).[17] There are lots of genetic mutations that occur in patients with HCC. In close to 80% of patients with HCC, the tumour develops in patients with background LC, and this is irrespective of the cause of the LC.[18] The association between LC and the development of HCC have long been known, nevertheless, the ways through which LC transforms into HCC have yet to be fully understood. The risk of development of LC into HCC is greatest with the macronodular type of LC compared with the micronodular type in about 15%–55% of all cirrhotics.[2] One possible explanation for the close aetiological association between LC and HCC is that cirrhosis itself is a pre-malignant condition. The hyperplasia of hepatocytes in patients with LC over time progress to HCC even in the absence of additional causal factors, such as chemical or viral carcinogens.[2] Another possible mechanism is that patients with LC are susceptible to so many environmental carcinogens.[19] The reason for this might be due to the rapid liver cell death and regeneration in which cells that are undergoing rapid division eventually become cells that promote the development of cancer, these cells become susceptible to DNA changes by chemical or other agents present during cell division.[19] In addition, rapid cell division and regeneration may also interfere with the DNA repair process in cells resulting in abnormal DNA alterations being carried over to new daughter cells, and are thereby fixed in the progeny. These are processes that occur independent of the original cause of the LC.

MECHANISM OF HEPATITIS B VIRUS-INDUCED HEPATOCELLULAR CARCINOMA

HBV is a carcinogenic virus and can cause HCC in the presence or absence of LC. A very close association exists between chronic HBV infection and HCC in sub-Saharan black Africans and Chinese Asian patients. Patients from these two areas carry between 56% and 90% evidence of past infection of HBV.[20-23] The HBV genome does not contain a recognised oncogene. The virus most likely causes HCC through both direct and indirect mechanisms in the liver. The indirect pathway occurs through the chronic hepatocyte injury induced by HBV resulting in continuous ongoing necroinflammation and cell death and regeneration of new cells with overall increase in liver cell turnover rates. This process may eventually lead to the accumulation of toxic substances that may induce mutations in the liver cell genome leading to expansion of affected cells (clonal expansion) and subsequent HCC. Chromosomal abnormalities and a loss of alleles are common and are found in about 50% of the nodules of patients with LC, and direct occurrence of HCC has been observed in these nodules.[24]

In addition, HBV infection can directly cause HCC by HBV-DNA integration into host cellular DNA through transcriptional activation of growth regulatory genes as well as the effects on apoptosis, cell signalling, and DNA repair.[24] The integration of HBV-DNA into the host DNA is a phenomenon found in 85% or more of HBV-related HCC.[24] This integration appears to target sites regulating cell signalling, proliferation and viability. In the process, oxidative stress occurs and increases the chances for the development of both cirrhosis and the integration of the virus.[24] The occurrence of mitotic transformation to HCC takes place when these genetic alterations appear to favour the growth of the affected mutated cells.[25]

THE ROLE OF THE HEPATITIS B VIRUS X GENE

There are evidences to suggest that the pathogenetic mechanism which is responsible for HBV-induced HCC has to do with the HBV X gene and its products.[25] This gene is commonly integrated into the human DNA in patients that are infected and become induced to HCC. In fact, the gene is expressed in approximately 70% of patients having HBV induced HCC.[24] The HBx gene is a transcription activator of both host and viral regulatory elements, including c-myc, c-jun, c-fos, TP53, AP-1, nuclear factor κB and SP-1.[26] This gene can bind with the P-53 gene that repairs damaged cells, thereby inhibiting P-53-induced apoptosis and interfering with liver cell mechanism that repair DNA, regulation of the cell cycle and suppression of cancerous growth.[26] This HBx gene also modulates the transcription of methyltransferases, that are responsible for the regional methylation of DNA which eventually stop tumour suppressor gene or cause a global

hypomethylation that leads to chromosomal instability.[27] There are evidences that suggest the HBx gene protein lead to an increased expression of telomerase reverse transcriptase and telomerase activity, both of which prolong the life span of liver cells and contribute significantly to liver cell transformation to HCC.[27] The HBV spliced protein is expressed in chronic HBV infection and may induce apoptosis and modulate signalling through the transforming growth factor pathway, promoting fibrosis and malignant transformation.[28]

THE MECHANISM OF HEPATITIS C VIRUS-INDUCED HEPATOCELLULAR CARCINOMA

The number of people that are chronically infected with the HCV virus is about 71 million worldwide of which 20% will progress to LC.[29,30] The percentage of CLD patients with HCV infection in Nigeria appears to be high, a study in the densely populated Lagos metropolis reported a prevalence of 12%.[31] However, the prevalence rate of HCV in Nigeria according to the Federal Ministry of Health statistics is 1.1%.[32] Another population-based study in North central Nigeria, also reported a prevalence of 1.0%.[33] The annual rates of occurrence of HCC in HCV induced LC is 4.5%.[34] HCV-induced LC commonly occurs in a liver that has undergone some features of minimal inflammation before progression to LC.[2] HCC arises in a cirrhotic liver induced by HCV in about 70%–90% of cases.[19] The mechanism of HCC carcinogenesis in HCV induced LC is as a result of increased hepatocyte turnover from the chronic inflammation and resulting injury and regeneration of liver cells as well as an ensuing oxidative DNA damage.[29] This cascade of inflammation, regeneration and oxidative DNA damage creates a microenvironment that results into the emergence of genetic and epigenetic alterations that, if allowed to proceed for 10 years or more will ultimately lead to the emergence of LC from which HCC can develop. Another factor that can lead to reactive oxygen species, chronic hepatic inflammation, and liver fibrosis is steatosis, which may also progress to HCC.[35] Oxidative stress is a key factor for both LC and HCC to develop, this oxidative stress activates stellate cells and is a key factor that promote the development of fibrosis through the activation of cell signalling pathways that contribute to cellular transformation.[36] There are some changes that are also central to the hepato-carcinogenic effects of HCV. These include the cellular regulatory pathways that are linked with the proliferation and apoptosis and suppression of host immune responses.[37] It is therefore not unlikely that some of these pathways are involved in the development of HCC in addition to others that are direct causes. In addition, there are evidences that liver steatosis and diabetes mellitus are important contributing diseases that promote the development of HCC in HCV induced well compensated LC.[38] Furthermore, the additional risk of co-infection with HBV in HCV-induced LC portends an increased risk for the development of HCC,[39] particularly if these patients have elevated serum ALT and hepatic steatosis,[40,41] Patients with HCV-induced LC that achieve sustained virological response have reduced chances of developing HCC.[42] Studies on the occurrence of HCC after direct-acting anti-viral treatment are however still controversial.[43-45]

THE ROLE OF AFLATOXIN INDUCED HEPATOCARCINOGENESIS

Exposure to aflatoxin (AFB1) plays a crucial role in the occurrence of HCC in developing countries particularly if the individual has chronic HBV infection as this could increase the risk up to 30 times greater.[46] About 30% of all cases of HCC globally are due to exposure to AFB1.[47] The pathogenesis of how AFB1 induces HCC begins with epoxidation of AFB1-8, 9-epoxide by CP450 enzyme. AFB1binds the guanine bases on the third base of codon 249 of the p53 gene to form AFB1-N7-guanine. AFB1 impacts on p53 suppressor gene which prevents cell cycle progression.[47] This type of mutations is common in regions with high AFB1contamination. HBV probably induce the conversion of AFB1 to AFB1-8, 9-epoxide by specific enzyme CP450s in both direct and indirect ways. In one study from South Western Nigeria, the prevalence of codon 249 of p53 mutation was found to be very high among HCC patients and particularly those that had HBV infection.[48]

SIGNS THAT RAISE SUSPICION OF MALIGNANT TRANSFORMATION IN A PREVIOUSLY COMPENSATED CIRRHOTIC LIVER

The signs that LC has decompensated due to malignant transformation include rapid deterioration in the liver function, new onset (refractory) ascites, acute intra-abdominal bleeding, increased jaundice and weight loss or fever. Other signs are new onset hepatic encephalopathy, variceal bleeding and right upper quadrant abdominal pain or the sudden development of erythrocytosis in a stable LC with previously normal packed cell volume.[49] Examination may reveal a palpable liver mass that is hard and tender with irregular liver surface. Other findings might include splenomegaly, ascites, jaundice and a hepatic bruit on auscultation. A study conducted in North America reported that 57.8% of HCC occurred on a background of LC.[50] The mean survival in these patients with background LC was 6.4 months compared with 16.7 months in those without background LC.[50]

In terms of pathological types, HCC may present as a unifocal, multifocal or diffusely infiltrative tumour.[51] All the patterns of HCC usually demonstrate broad potential for vascular invasion. When there is background LC, HCC usually arises from a malignant transformation of a regenerative nodule. There is stimulation of angiogenesis, and the tumour receives abundant arterial vascularisation.[52] The mean tumour duplication time is about 20 days.[53] This time decreases as the tumour mass

increases. When the tumour mass is up to 3 cm in diameter, HCC is generally well differentiated, encapsulated and has low potential for blood vessel invasion. When it reaches an approximate size of 5 cm, the nodule begins to lose differentiation and to exhibit microscopic vascular invasion acquiring capacity to generate metastases.[52]

NATURAL HISTORY, SCREENING AND DIAGNOSIS OF MALIGNANT TRANSFORMATION IN A CIRRHOTIC LIVER

At diagnosis of HCC, only a minority of cases are potentially curative. When curative operative intervention is not possible, the tumour usually grows as a cancer that reduces the liver function and generates intra- and extra-hepatic metastases; mainly to the lungs and bones.[51] With distant metastasis, death occurs at a mean time of 10 months. The causes of death are due to tumor cachexia, hemorrhage from esophageal or gastric varices, hepatic insufficiency and more rarely from hemoperitoneum secondary to tumour rupture.[51] A study done in South Western Nigeria on patients with HCC reported an overall median survival time of 20 days.[14] Median survival in those with CTP score C was 14 days. Factors associated with overall survival were; older age, female sex, abdominal pain, jaundice, elevated creatinine, hyponatremia, elevated bilirubin, ALT, and aspartate aminotransferase.[14] Patients that had risk factors for HCC should undergo periodic screening to detect the occurrence of the tumour early. This class of patients includes; cirrhotic patients in CTP classes A/B, cirrhotic patients in CTP class C awaiting liver transplantation (LT), those with intermediate to high risk of developing HCC using the PAGE-B score [Table I].[54]

Recommendation for screening for HCC in Nigeria includes: All HBsAg-positive individuals >20 years including CHB patients in the inactive phase, individuals with positive antibody to HCV or elevated serum HCV RNA, patients with LC from any cause, individuals with a positive family history of HCC and those with elevated alpha-feto protein >20 ng/ml.[55]

Table I: Page B score for prediction of hepatocellular carcinoma in Caucasian chronic hepatitis B patients under treatment with entecavir or tenofovir

Age (years)/ allotted score	Gender/ allotted score	Platelet/(mm^3)/ allotted score
16-29: 0	Female: 0	≥200,000: 0
30-39: 2	Male: 6	100,000-199,999: 6
40-49: 4		<100,000: 9
50-59: 6		
60-69: 8		
≥70: 10		

The Page B score makes use of three parameters; age, gender, and platelet count and are scored as above. The 5-years cumulative probability of hepatocellular carcinoma in patients with low (≤9), medium (10-17) and high (≥18) Page B score are 0%, 3%, and 17%, respectively

The cost-effectiveness of screening has been widely demonstrated in one study.[2] In addition, some studies suggest that HCC screening would confer increased survival in patients with LC.[2]

Ultrasonography

The utilisation of ultrasonography for screening is widely available and also relatively cheap. Its sensitivity varies from 60% to 80%, with specificity >90% in patients with cirrhosis.[56] It is therefore a method of choice to screen for HCC in patients with LC, and should be performed every 6 months. The disadvantage of using ultrasonography is that detection of HCC on a background of a cirrhotic liver is challenging particularly in cases of a liver with coarse echo texture which may impair the identification of small tumours. It is also highly dependent on the expertise of the operator and quality of ultrasound equipment used.

Alpha-fetoprotein

It is the most widely used tumour marker for the diagnosis of HCC. AFP is synthesised by the liver and yolk sac during foetal development. Normal adult value is 10–20 ng/ml. Serum levels >400 ng/ml is regarded as significant while levels >1000 ng/ml is diagnostic of HCC. Issues with the use of AFP in LC to diagnose HCC is that fluctuating levels may reflect flares in HBV/HCV infection, exacerbation of the underlying liver disease or malignant transformation to HCC.[57] Also, about 20% of HCC do not secrete AFP and only a small proportion of tumour in the early stage presents with abnormal AFP. [36] The American Association for the Study of Liver Disease (AASLD) recommends ultrasound scan with or without alpha-feto protein every 6 months as a screening tool for the detection of HCC.[57]

Radio-diagnosis

The definitive diagnosis of HCC is achieved through contrast-enhanced computer tomography (CT) scan of the abdomen and/or magnetic resonance imaging (MRI). Contrast-enhanced CT and MRI scans usually reveal a nodule with important enhancement in the arterial phase (hyper-vascularity). In the portal and late phases, HCC usually undergoes rapid elimination of the contrast (wash out), becoming hypodense in comparison with the rest of the liver parenchyma.[51] Sensitivity of CT scan is 68% and its specificity is 93%.[58] MRI presents similar results, with a sensitivity of 81% and a specificity of 85%.[58] AASLD developed the following recommendations for patients with cirrhosis and a liver nodule: (a) nodules smaller than 1 cm in diameter identified by ultrasonography should be followed at 3 monthly intervals, and if there is no evidence of growth in 2 years, the nodule should be considered as a regenerative nodule: (b) nodules >1 cm in diameter should be evaluated by contrast enhanced dynamic studies – either CT or MRI-in order to identify typical radio-diagnostic characteristics of HCC. (b1) if typical malignant features are identified, there is no need for additional methods and the diagnosis of HCC is established; (b2) if there are no typical features in the dynamic study, a second

dynamic test or an ultrasound guided liver biopsy study may be considered.[56,57] Percutaneous HCC biopsy should be avoided as there may be tumour spread in the percutaneous needle track and this represents about 3% risk.[59] In addition, there is the risk of haemo-peritoneum from the puncture from rupture of a nodule of the liver and possible risk of death.[60] When HCC is diagnosed, chest CT scan is recommended for staging.[59] The occurrence of extra-hepatic metastases is a contraindication to liver resection and transplantation (LT).[59]

STAGING OF HEPATOCELLULAR CARCINOMA OCCURRENCE IN A CIRRHOTIC LIVER

The most widely used staging method is the Barcelona Clinic Liver cancer (BCLC) staging that puts into consideration the tumour size, CTP score, performance status of the patient and the presence or absence of portal invasion [Figure 1]. The BCLC stage helps to prognosticate patients and also to determine the modality of treatment that best suits each stage.

TREATMENT

There have been recent advances in the treatment of HCC [Figure 2]. The treatment can be divided into curative and non-curative. The curative treatments are: Surgical resection, orthotopic LT and ablative technique like thermal ablation. Non-curative therapies attempt to prolong survival by slowing tumour progression and they include: Trans-arterial chemoembolisation (TACE), trans-arterial radioembolisation, stereotactic body radiation therapy and systemic chemotherapy.

CURATIVE THERAPIES FOR HEPATOCELLULAR CARCINOMA

Resection

Hepatic resection is the treatment of choice for patients with a solitary tumour and preserved liver function (CTP Class A). Liver resection is recommended for a single HCC nodule of any size and in particular for tumours >2 cm, when liver function is preserved and sufficient remnant liver volume is maintained. HCC with 2 or 3 nodules within the Milan criteria (one single node <5 cm or 3 nodules <3 cm and no extra-hepatic metastasis) may be eligible for resection depending on the liver function, performance status and remnant liver volume.[61] For patients with a single nodule, preserved hepatic function and without portal hypertension (normal bilirubin, hepatic pressure gradient <10 and platelet count >100,000/cmm), surgical resection offers low perioperative mortality and survival rate of up to 70% at 5 years,[56,57] [Table II]. Macrovascular invasion is a contraindication to resection; peri-operative mortality rate is up to 3%.[61]

Liver transplantation

Is an highly effective and efficient treatment for early HCC because it offers optimal treatment for both the underlying disease and the tumour and is associated with excellent long term survival rate for HCC within the Milan criteria occurring in the setting of a decompensated liver disease.[62] The majority of patients whose sum of the size of the largest HCC with the total number of tumours that does not exceed seven (up to seven criteria) may undergo neoadjuvant treatment by TAE or TACE. Such treatment may be able to control and even decrease tumour mass in several patients (down-staging). A similar group of patients who may undergo TAE or TACE for the purpose of decreasing tumour disease are a large proportion of patients with HCC exceeding the Milan

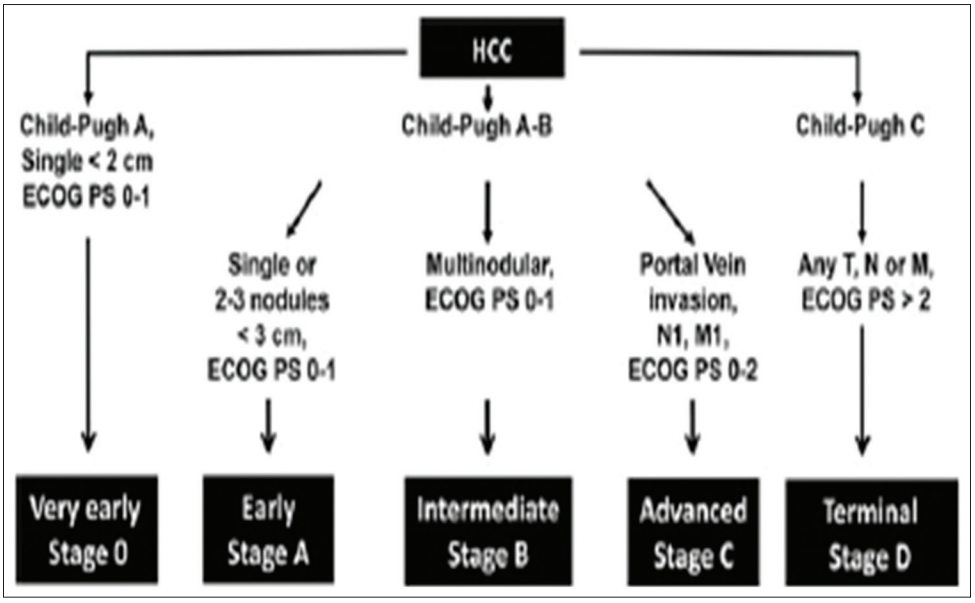

Figure 1: Barcelona Clinic Liver cancer hepatocellular carcinoma staging T: Tumor, N: Node, M: Metastasis, PS: Performance status

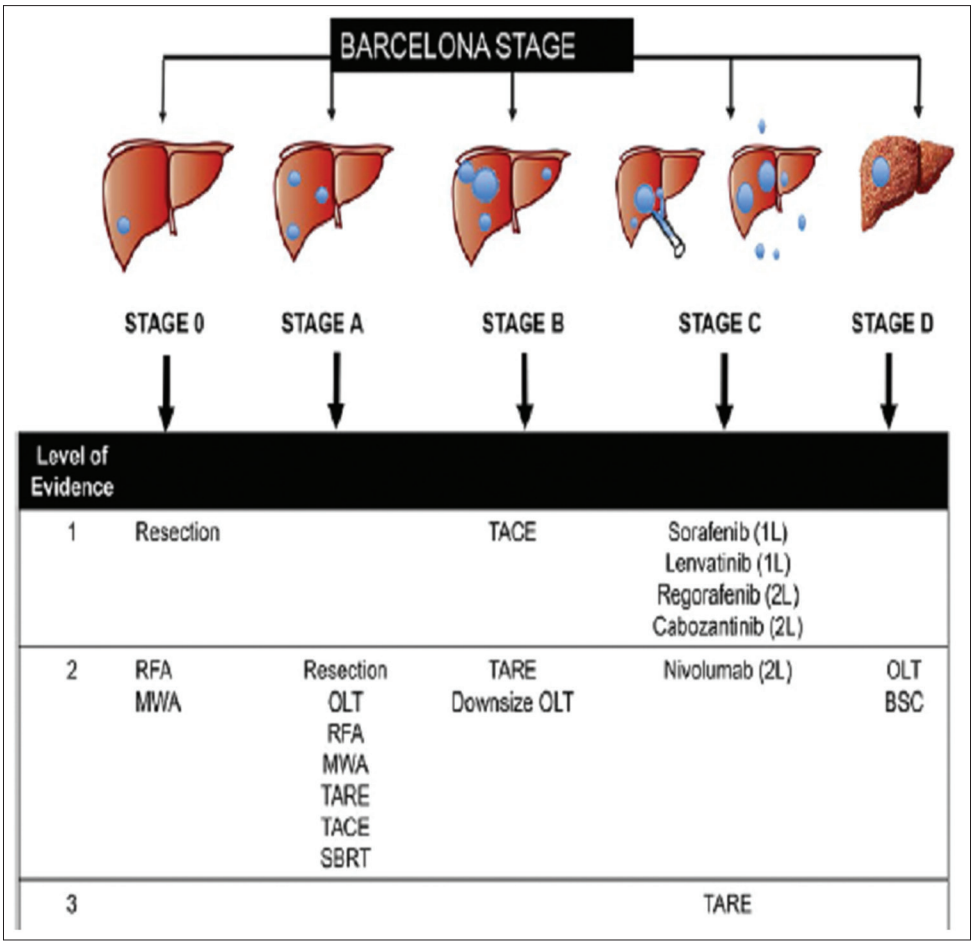

Figure 2: *Treatment recommendation according to BCLC stage.* BCLC: Barcelona Clinic Liver cancer *RFA*: *Radiofrequency ablation, MVA*: Microwave *ablation, OLT*: *Orthotopic liver transplantation, TARE*: *Transarterial radioemboliation, TACE*: *Transarterial chemoembolisation, SBRT*: *Stereotactic body radiotherapy, BSC*: Best supportive care*, 1L*: *1st line therapy, 2L*: *2nd line therapy. Level of* evidence: *Level 1 – There is evidence from at least one randomised control trial. Level 2 – There is evidence from at least one well-designed cohort study or case–control study. Level 3 – Opinions of respected authorities based on clinical experience, descriptive studies* or reports of expert committees

Table II: Criteria for hepatocellular carcinoma resection in a cirrhotic liver

No distant metastasis
CTP class A
Absence of portal hypertension
Platelet count >100,000/cmm
MELD score <11
ECOG (0 or 1)
Liver remnant estimated by CT volumetry of the liver larger than 50%,in cirrhotic patients

CTP: Child-Pugh, ECOG: Eastern Cooperative Oncology Group performance status, MELD: Model for end stage liver disease, CT: Computer tomography

Criteria but still included in the University of California San Francisco Criteria (one tumour ≤6.5 cm, three tumours with the largest up to ≤4.5 cm, and a total tumour sum diameter ≤8 cm). If the tumour disease responds well to neoadjuvant treatment and is reduced to fit within the Milan Criteria (down-staging), these patients may be listed for LT.[52] Recurrence of HCC following transplantation has been estimated to be 11%–18%.[55] Factors associated with recurrence include AFP >50 ng/ml pre-transplant and poorly differentiated tumour on histology. Median recurrence time is 20.5 months.[63]

Ablation

It is a therapeutic option that has rapidly grown in the last decade. It is considered potentially curative. Ablation of the tumour can be achieved by injecting chemical substances such as ethanol, acetic acid and saline at 100°C or by modifying local tumour temperature using radiofrequency, microwave or cryotherapy.[57] It is considered a treatment of choice for patients in BCLC A who are not candidates for surgical intervention. Some randomised control trials (RCTs) have shown the superiority of radiofrequency ablation (RFA) over ethanol injection in terms of survival particularly in BCLC stage A with nodules between 2 cm and 4 cm.[64] Areas of tumour location that are contraindicated for RFA include tumour near the main biliary tree, abdominal organs, or the heart.[57]

NON-CURATIVE THERAPIES

Trans arterial chemoembolisation

It is the first treatment of choice in patients with compensated liver disease and a large or multifocal HCC without vascular invasion or extra-hepatic spread.[61] Intra-arterial treatment promotes ischemic necrosis (coagulation necrosis) in the tumor.[52] It is utilized for patients awaiting LT and also as palliation for patients not suitable for resection or LT. It is contraindicated in patients in CTP Class C. Chemotherapy emulsioned with lipiodol is injected into the tumour followed by vascular stagnation achieved with embolisation. The most commonly used agent either singly or in combination are epirubicin or doxorubicin, cisplatin or miraplatin.[65] The rationale for TACE is that intra-arterial injection of a cytotoxic agent followed by embolisation of the tumour-feeding blood vessel will result in strong cytotoxic and ischaemic effect targeted to the tumour.[61] Technical advancement including embolisation in a super-selective manner to minimise ischaemic injury in non-tumorous tissues have improved the outcome in TACE.[57] The survival benefit of TACE compared with the best supportive care was shown in a RCT in which treatment response was an indicator of survival.[66]

Systemic therapies

Sorafenib a tyrosine kinase inhibitor is the treatment of choice for advanced HCC with vascular invasion and/or extra-hepatic metastasis with improved survival outcome than supportive care.[57] It has demonstrated a survival benefit of approximately 3 months over the use of placebo.[67] Another trial showed a median overall survival of 10.7 months compared with placebo of 7.9 months.[61] Sorafenib is well tolerated and its common side effects include diarrhoea, and hand-foot skin syndrome. Regorafenib is a multikinase inhibitor and has been studied as a second line agent for patients who progress on Sorafenib. A study has shown a median survival of 10.6 months compared with 7.8 months in the placebo group. [57] Immune check point inhibitors targeted against cytotoxic T lymphocytes antigen-4 programmed death-1 ligand are been investigated in combination therapy.[57]

MULTIDISCIPLINARY MANAGEMENT OF HEPATOCELLULAR CARCINOMA

The management of HCC requires a multi-disciplinary approach including hepatologist, diagnostic and interventional radiologists, surgical oncologists, pathologists, transplant surgeons, radiation oncologist and palliative nurses.

PALLIATIVE CARE

Because of the dismal prognosis of patients with advanced HCC with life expectancy of 3–4 months, management is largely symptomatic and no tumour directed therapy is indicated. Pain management should be with acetaminophen for mild pain and opiods for moderate-to-severe pain. Non-steroidal anti-inflammatory drugs should be avoided due to the risk of gastrointestinal bleeding, nephrotoxicity and decompensation of ascites.[68] Nutritional intervention should be considered in cases of low energy intake.

CONCLUSION

The diagnosis of malignant transformation in a cirrhotic liver requires a high index of suspicion and it is easily detected through appropriate surveillance. The importance of HCC surveillance should be emphasised in resource poor countries to be able to detect patients in the early stages of the disease which has a better prognosis than the advanced stages.

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