A 52-YEAR-OLD MALE WITH MALIGNANT TRANSFORMATION OF A CIRRHOTIC LIVER - A Case Illustration and Review

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PRESENTATION OF CASE

We present Mr A.F, a 52-year-old married man of Christian faith and Yoruba Ethnicity. He is a known patient of the Gastroenterology Unit of the Department of Medicine, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife who was being managed for Hepatitis B induced Liver Cirrhosis. The patient had defaulted regular clinic visits for one year prior to this presentation.
He presented at the Accident and Emergency Department of this hospital with right upper abdominal pain of a week duration.

The patient had been in his usual state of health until a week to presentation when he developed insidious, sharp, constant right upper abdominal pain that did not radiate to any other part of the body. The pain worsened a day to his presentation, there were no known aggravating or relieving factors, and the pain was said to be severe enough to prevent him from pursuing his usual daily activities.
There was progressive abdominal distention in association with the pain. The patient also experienced nausea and three episodes of vomiting. Vomitus contained recently ingested meal but no blood. There was easy fatigability but no loss of consciousness. There was no history of pedal swelling or early morning facial puffiness.
There was no haematemesis, passage of melena, or haematochezia. No constipation nor fever, no yellowish discolouration of the sclera. There was no history of consumption of herbal preparations.

The patient was prescribed Tenofovir Tablets for his Chronic HBV infection. However, drug compliance could not be ascertained prior to his presentation. His last clinic attendance was one year ago due to unexplained reasons.
The patient had no past medical history of Hypertension, Diabetes Mellitus or Peptic Ulcer Disease. He had upper gastrointestinal endoscopy and oesophageal band ligation performed in this facility a year prior to his presentation (before he defaulted) on account of upper gastrointestinal bleeding. There is no history of any major surgery. He was transfused once, following the episode of upper GI bleeding. The blood was adequately screened.
At presentation, he was not on any medication (asides the prescribed Tenofovir) and had no known medication allergies. He is married in a monogamous setting to a 45-year-old school teacher. He does not consume alcohol or tobacco in any form.
Review of systems yielded no additional information.

Examination revealed a conscious man in painful distress, febrile with an axillary temperature of 37.8˚C, pale, anicteric but not dehydrated. There was no finger clubbing, no asterixis or pedal oedema. His abdomen was uniformly distended moved with respiration, and there was right hypochondrial tenderness. Liver, spleen and kidneys were not palpably enlarged. The liver span was 6cm. Ascites was demonstrable by fluid thrill, the abdominal girth was 100cm, and aspirate yielded frank hemorrhagic fluid. Bowel sounds were normoactive. The digital rectal examination revealed a mildly enlarged prostate over which the rectal wall was freely mobile. The examining finger was stained with brown faeces. He had tachycardia with a pulse rate of 104bpm, regular and of normal volume. The radial arterial wall was not thickened, and there was no locomotor brachialis. Blood pressure at presentation was 112/80mmHg. First and Second heart sounds were heard without any murmurs or added sounds. Other systems were essentially normal. The patient weighed 70kg on examination.

ASSESSMENT/CLINICAL IMPRESSION

Clinical findings from the history and examination yielded the following assessment
i. Decompensated Liver Cirrhosis HBV-associated; keep in view Malignant Transformation of a Cirrhotic liver
ii. R/O Spontaneous Bacterial Peritonitis
The patient likely had a Cirrhotic Liver with Bleeding from a nodule resulting in Hemoperitoneum. The possibility of Malignant Transformation must be ruled out.

MANAGEMENT PLAN

An urgent PCV is required for a patient of this nature. PCV done was 20%. Random blood glucose was also requested which was 6.4mmol/L. Double Intravenous line access was immediately secured, and three units of fresh whole blood (grouped and crossmatched) was transfused. 2 units were transfused on the day of presentation, 1 unit was transfused a day later.

Blood samples were collected for Full blood count and Erythrocyte Sedimentation Rate, Electrolytes, Urea and Creatinine, Liver Function Tests (including serum protein), Clotting profile, Serum alpha-fetoprotein, Malaria parasites and Blood culture. Urine was collected for Microscopy, Culture and Antibiotic sensitivity testing. Tapped haemorrhagic ascitic fluid was also sent for laboratory analysis. Abdominal ultrasound, chest X-ray and Triphasic Abdominal CT scan orders were placed.

The patient was maintained on Tab DF118 20mg b.d; IV Rocephin 1g 12hourly; Tab Rabeprazole 20mg b.d; IV Fluid 4.3% D/S – 10% D/W 1L 8hourly; IV vit K 10mg daily*5/7; Susp Lactulose 10mls b.d; continue Tab Tenofovir 300mg daily

Patient's vitals were monitored closely, and he was transferred to the medical ward from the Accident and Emergency centre following transfusion and investigations.

Table 1: Laboratory Data

Investigation	On admission	Result 2	Result 3
E/U/Cr	Na+: 122mmol/L K+: 4.1mmol/L HCO3-: 21mmol/L Cr: 88micromol/L Urea: 5.0mmol/L		
LFT	B1: 42micromol/L B2: 29micromol/L ALP: 198(60 -170)IU/L AST: 92 (<12) IU/L ALT: 39 (<12) IU/L		
Serum Proteins	Protein: 62g/L Albumin: 37g/L		
PCV	20%	31%	33%
INR	4.5	2.7	1.6
Serum AFP	90ng/ml (<=10.9ng/ml)		
Blood leucocyte count	5,100 cells/mm3 Neut: 51% Lymp: 49%		
Platelet count	29,000 cells/mm3	40,000 cells/mm3	89,000 cells/mm3
Film for MP	1+ of Trophozoite of P. falciparum		
HBV-DNA (viral Load)a	4,816,030 ctvopies/ml		
Ascitic Fluid m/c/s, Urine m/c/s, Blood culture	Yielded no growth		
CXR	Normal Findings		

[a]The HBV DNA (Viral load) was done before the commencement of Tenofovir

IMAGING STUDIES

Abdominal USS:
The Liver measured 10.6cm, irregular outline, coarse parenchymal echotexture. Spleen measures 10.15cm. Copious ascites with homogenous echo.

Triphasic Abdominal CT scan:
Shrunken Liver, Multiple fairly rounded non-enhancing hypodense nodules in the liver, with collapsed/ruptured nodule in segment [6], Massive Ascites. Impression: Chronic Liver Disease with possible Malignant Transformation

CLINICAL DIAGNOSIS

A diagnosis of Malignant transformation of Chronic Hepatitis B induced Liver cirrhosis was made and the patient was assigned a Barcelona Liver Cancer staging system (BCLC) class C

RATIONALE FOR DIAGNOSIS

A detected nodule in the setting of a Cirrhotic liver is highly suggestive of Hepatocellular carcinoma. This can be confirmed via a targeted liver biopsy.

SUMMARY OF MANAGEMENT

The patient was counselled for a targeted ultrasound-guided liver biopsy for which he refused.
He was then placed on Tab Sorafenib 400mg b.d.
The patient's abdominal pain subsided on day two of admission. The patient was treated for malaria and fever, which subsided on the 3rd day of admission. He had 3 unit of Fresh whole blood (post-transfusion PCV 31%), and he was thereafter placed on haematinics without folate. He had five units of fresh frozen plasma, a repeat INR of 1.6 and maintained on IV Vit K for five days. He also had four units of platelet concentrate and repeat platelet count was 89,000cell/mm3. He was on continued on Tab Tenofovir and commenced on Sorafenib

DISCHARGE SUMMARY

The patient was discharged 27 days after admission. His vitals on discharge were: Pulse rate- 82bpm, regular and of normal volume; Blood pressure- 128/80mmHg; Respiratory rate was 20cpm. The abdominal girth was 80cm, and he weighed 62kg.
The patient was ambulating well and was given an appointment to be seen in the Gastroenterology outpatient clinic in two weeks.

FOLLOW UP CLINIC VISIT

The patient was seen in the gastroenterology outpatient clinic of this hospital two weeks after discharge. He has no fresh complaint and was doing well on Tab Tenofovir and Tab Sorafenib.
He was given another clinic appointment in two months following this clinic visit.

DISCUSSION- A REVIEW OF THE RELATIONSHIP BETWEEN CIRRHOSIS AND MALIGNANT TRANSFORMATION

Cirrhosis is a pre-malignant condition associated with fibrosis and nodular regeneration[1]. There is abundant evidence of a causal relationship between cirrhosis and hepatocellular carcinoma. It is important to emphasise that the aetio-pathology of malignant transformation in cirrhosis shows some differences between high- and low-incidence regions of hepatocellular carcinoma[2]. In regions of high incidence of hepatocellular carcinoma, cirrhosis is typically asymptomatic, usually of the macronodular variety, and the predominant aetiology is chronic hepatitis B virus infection[2]. However, in regions of low-incidence of hepatocellular carcinoma, the cirrhosis is usually long-standing and symptomatic, more commonly macronodular, although micronodular cases have been reported, and is caused by chronic hepatitis C virus infection, chronic consumption of alcohol over many years, metabolic syndrome, or hereditary hemochromatosis[2]. Less commonly, hepatocellular carcinoma develops in the absence of cirrhosis, thus lending support to a direct carcinogenic effect of some etiologic agents.

HEPATITIS B AND HEPATOCELLULAR CARCINOMA

The relationship between Hepatitis B virus and malignant transformation could be the result of a direct insult to cellular genetic integrity or indirectly through long-standing chronic inflammation. The direct mechanism of hepatitis B induced malignant transformation involves an integration of the viral DNA into host cellular DNA; transcriptional activation of host growth regulatory genes by hepatitis B virus-encoded proteins; and effects on apoptosis, cell signalling, and DNA repair[3,4]. Chronic inflammation provides fertile soil for neoplasia and is an indirect route by which HBV infection can cause malignant transformation following cirrhosis. Cirrhosis is a major risk factor for tumour formation in patients with chronic hepatitis B and C virus infection[4]. The pathogenesis of malignant transformation of the cirrhotic liver in the setting of chronic HBV or HCV infection does not involve the integration of viral DNA into host cellular genetic material but rather, increased liver cell turnover induced by concurrent injury and regeneration (repair) of cells in a background of chronic inflammation featuring oxidative DNA damage, fibrosis and cirrhosis[5]. In some patients, the presence of HBV can be demonstrated within the tumour even when seronegative for Hepatitis B virus[6].

REGIONAL DIFFERENCES IN THE INCIDENCE OF CIRRHOSIS AND HCC

There is often a co-existence of hepatic cirrhosis and hepatocellular carcinoma. In most populations, cirrhosis is far more prevalent, and diagnosis of hepatocellular carcinoma is seldom made[7]. However, the reverse is true for populations in sub-Saharan Africa and Southeast Asia where hepatocellular carcinoma occurs more frequently and may surpass cirrhosis in incidence in some areas[7]. Nevertheless, considerable evidence supports the existence of a causal relationship between cirrhosis and HCC, albeit one that differs between low- and high-risk regions of the tumour[8].

Patients with underlying cirrhosis in populations at low risk of HCC are usually at an advanced stage when diagnosed[2]. This is evidenced by the observation that patients with both the tumour and cirrhosis are more likely than those with the tumour alone to be jaundiced, to have ascites, and to bleed from oesophageal varices[9]. Also, clinical laboratory investigations in these patients are more likely to reveal a prolonged prothrombin time, a low serum albumin concentration, and raised serum bilirubin and aspartate aminotransferase levels[9]. However, these clinical findings are seen patients with both HCC and cirrhosis as well as patients with isolated HCC who are of sub- Saharan Black African or Chinese descent [4,5,10-12]. Indeed, tests of hepatic function and damage are similar in Africans with HCC with and without cirrhosis[8,13]. In the presence of cirrhosis, HCC is far more common in men than women[3,14,15]. However, when the tumour occurs in a non-cirrhotic liver in high-risk regions, male predominance is less striking but still prevalent [5,16].

Literature suggests that between 60-85 % of sub-Saharan African and Chinese patients with co-existing cirrhosis and HCC possess serological markers of current HBV infection, and antigenic markers for the virus can often be detected in the cirrhotic liver [12, 16, 17]. A more modest percentage of patients with HCC in these populations is chronically infected with HCV[18]. However, aetiology does not appear to influence the clinical picture, and there have been no recorded specific differences in the clinical manifestations of cirrhosis or HCC between patients chronically infected with HBV or HCV or with patients with prolonged alcohol abuse.

It is essential to recognise that HCC can rarely occur outside of a background of recognisable risk factors[19]. In the remote areas of sub-Saharan Africa, where the highest incidence of HCC in the continent has been reported, evidence of alcoholic liver disease is rarely present[2]. Indeed, a history of chronic alcohol consumption may be obtained. However, the beer consumed often has a low alcohol content[2], and it may be useful to obtain some information about local beer consumption. Locally produced beer may have a high iron content as a result of local brewing of the liquor in iron drums or pots, which promotes leaching of iron into the beer and subsequent iron overload of the liver following consumption[2,20]. It is clear that the cause of HCC in such a case is not alcohol consumption but rather iron contamination causing iron overload[19]. More recently, a small, but increasing cohort of African males with HCC have been reported to have evidence of conventional alcohol-induced liver disease+. Additional aetiologies of cirrhosis such as Wilson's disease, hereditary haemochromatosis, and primary biliary cirrhosis are seldom encountered in sub-Saharan African populations[2]. Non-alcoholic steatohepatitis is also a risk factor for cirrhosis and HCC in obese patients[21].

A diagnosis of HCC (regardless of the presence or absence of co-existing cirrhosis) in patients in sub-Saharan Africa is often made at a young age [4,12,22]. This suggests that the causative agent or agents of one or both diseases are operational at an early age. Indeed, HBV infection is frequently acquired in early life this region [23,24].

MALIGNANT TRANSFORMATION IN THE CIRRHOTIC LIVER

The incidence of HCC is greatest in a cirrhotic liver. Several studies have supported this fact by showing that in up to 90% of patients with a diagnosis of hepatocellular carcinoma, the tumour develops within a background of liver cirrhosis, regardless of aetiology of the cirrhosis [25-29]. Notably, hepatocellular carcinoma rarely occurs outside of a background of recognisable risk factors. An example of such exception is the fibrolamellar type of cancer which occurs without a history of cirrhosis or viral hepatitis[30].

It is worthy to note that even though the close association between cirrhosis and HCC has long been recognised, the precise mechanisms by which cirrhosis induces malignant transformation has not been completely elucidated. The risk of malignant transformation is greatest with macronodular cirrhosis. The proportion of patients with macronodular cirrhosis who develop HCC ranges, in different parts of the world, from 15 to 55%, although figures of between 40 and 55% are not uncommon [17, 19, 25, 28-30]. Macronodular cirrhosis is also likely to be present in long term abusers of alcohol, and this is further complicated by the development of HCC in 15–24 % of such patients. However, the reverse is the case for patients who have abused alcohol for a shorter duration where micronodular cirrhosis is more commonly seen, and the complication by HCC occurs in only 3–10% of patients[26,27,31].

There appears to be a direct relationship between the severity of liver cirrhosis and subsequent development of HCC. In up to 50% of patients with severe cirrhosis, the situation is often complicated by HCC compared to an incidence of 13% in those with moderate cirrhosis[32]. Interestingly, even in patients in high-incidence regions of HCC in whom the symptoms of macronodular cirrhosis may be absent or overlooked, the presence of the cirrhosis is often an incidental finding at autopsy or earlier on during histological diagnosis of the tumour[2].

Several propositions have been made regarding mechanisms for the causal relationship between cirrhosis and HCC. One possible explanation is that cirrhosis itself is a pre-malignant condition[2]. The hyperplasia of hepatocytes observed in a cirrhotic liver may over time result to dysplasia, anaplasia and frank neoplasia even in the absence of additional drivers of carcinogenesis. Indeed, this sequence of events is supported by the observation in experimental animals that almost all forms of cirrhosis are eventually complicated by HCC[32]. However, there are several reasons why the logic may be flawed. Firstly, if the mechanism described were universally applicable, then we would expect a direct relationship regarding the geographic distribution between cirrhosis and the development of HCC[2]. Now while this may hold for macronodular cirrhosis, the same cannot be said for micronodular cirrhosis. This is best exemplified in Central and Northern Europe where HCC is much rarer despite the high incidence of alcoholic micronodular cirrhosis, compared to sub-Saharan Africa region and China, where micronodular cirrhosis is seldom seen, and the number of cases of HCC equals or may exceed the number with macronodular cirrhosis [28,29]. Secondly, if it were true that hyperplasia would inevitably result in neoplasia, we would expect patients with cirrhosis and HCC to be older on the average compared to patients with cirrhosis alone; while this is true for western countries [20,28], it is not so for populations in sub-Saharan Africa and China[12]. Thirdly, if hyperplasia were inevitably complicated by neoplasia, we would expect a similar risk of development of HCC following all types of cirrhosis. However, this is not so in practice where the risk of development of HCC ranges from approximately 50% for patients with macronodular cirrhosis in sub- Saharan Black Africa to less than 1 % for primary biliary cirrhosis and cirrhosis in Wilson's disease, which have degrees of hyperplasia similar to that seen in alcoholic liver disease2. The relationship between cirrhosis and HCC is further complicated by geography. It has been shown that for patients with macronodular cirrhosis in sub-Saharan Africa, the risk of development of HCC is 44–54%, whereas in western countries the risk is only 15–25% [2]. For patients in such low incidence regions, the most critical determinants of malignant transformation in the setting of liver cirrhosis are male sex and increasing age (which is related to the duration of the cirrhosis) [9, 14]. Another proposed explanation for the mechanism of malignant transformation of the cirrhotic liver is that the presence of cirrhosis renders the individual susceptible to a variety of environmental carcinogens[7]. This is likely due to a higher than usual rate of hepatocyte turnover in the cirrhotic liver which acts as fertile soil for genetic insults because cells undergoing mitosis have a higher susceptibility to DNA alterations by chemicals and other mutagens/carcinogens. Moreover, rapid cell turnover rates result in mutations that overwhelm the rate of repair by DNA repair mechanisms. The result is the transmission of unrepaired DNA alterations to daughter cells. As per this explanation, the tumorigenic effects are presumably independent of aetiology of cirrhosis[2].

Finally, it is important to stress that HBV and HCV are carcinogenic viruses and can cause HCC independent of cirrhosis.

FIBROTIC CHANGES INDUCE TUMORIGENESIS IN LIVER

The liver is considered unique with regards to its response to injury as it undergoes regeneration and fibrosis concurrently[33]. As stellate cells and myofibroblasts produce growth factors including hepatocyte growth factor, interleukin-6 and WNT ligands, they drive fibrogenesis and promote angiogenesis. These changes, in turn, promote survival of activated hepatic stellate cells as well as preneoplastic hepatocytes, thus increasing susceptibility to tumorigenesis by promoting hepatocyte proliferation[33,34]. Furthermore, hepatic myofibroblasts also synthesise PDGF and TGF-β, thus fostering the growth and migration of pre-malignant hepatocytes[35]. Likewise, hepatic stellate cells secrete angiopoietin-1 which encourages angiogenesis, a prime requirement for tumorigenesis[36].

Additionally, with fibrosis comes a modification in the activity of inflammatory cells in the liver, a process induced by fibrotic changes. The result is a diminution in the activity of natural killer cells and T lymphocytes that generally contribute to tumour surveillance[37]. All of these tumour enhancing pathways work in concert with inflammatory signals such as reactive oxygen species and telomerase reactivation thereby contributing to malignant transformation[37].

CLINICAL FEATURES AND STAGING OF MALIGNANT TRANSFORMATION

The prognosis of patients with hepatocellular carcinoma is largely dependent on the degree of underlying liver cirrhosis and its complications[38,39]. The criteria for an ad-

equate staging system for hepatocellular carcinoma include relevant features such as characteristics of tumour prognosis as well as measures describing liver function[40]. Such a classification system would also ideally assign treatment modalities to each prognostic subclass[37]. It is worth noting that of several prognostic and staging systems for hepatocellular carcinoma that have been developed by various groups, only two – the Barcelona-Liver Cancer (BCLC) staging system and the Chinese University Prognostic Index (CUPI) have included tumour extent, liver function, and general condition in their system[41-43]. The BCLC staging goes even further to allocate evidence-based treatment strategies to each of the five resulting subclasses[42]. Endorsed by both the European Association for the study of the Liver and the American Association for Study of Liver Diseases, the BCLC is currently one of the most widely used staging and treatment systems in the management of hepatocellular carcinoma [37,44].

As per the BCLC system, treatment decision for hepatocellular carcinoma relies on the severity of the underlying liver cirrhosis, which is usually stratified according to Child-Pugh score [41,42,44]. The BCLC system is not without fault, however. Many have criticised the use of the Child-Pugh stage in the management of hepatocellular carcinoma because while only three classes A/B/C are used for staging, small but prognostically relevant increments within one class are not considered[41,45,46].

There is another system which addresses this issue by sub classifying patients with an intermediate stage of hepatocellular carcinoma using Child-Pugh points rather than Child-Pugh categories to assign patients to different prognostic subclasses[47]. The 'Albumin-Bilirubin (ALBI) grade' is another relatively new scoring system which assesses liver function in patients with hepatocellular carcinoma; it is based on serum albumin (synthetic function) and bilirubin (excretory function) and is comparable in performance to the Child-Pugh score while having the advantage of sub-stratification of the Child-Pugh class in prognostic classes[48].

Table 1: The Barcelona Clinic Liver Cancer (BCLC) system

Very Early Stage (o)	Single tumor <2cm Child-Pugh A Ps 0
Early Stage (a)	m Up to 3 tumours, all smaller than 3cm Child-Pugh A-B Ps 0
m Intermediate Stage (b)	Multinodular tumours Child-Pugh A-B Ps 0
Advanced Stage (c)	Portal invasion n1,m1 Child-Pugh A-B Ps 1-2
Terminal Stage (d)	Child-Pugh C Ps 3-4

Adapted from Chedid et al. (2017)21

Table 2: Child-Pugh Scoring system

	Points		
Variable	**1**	**2**	**3**
Encephalopathy	None	Stage I-II	Stage III-IV
Ascites	Absent	Controlled	Refractory
Bilirubin - mg/dL	<2	2-3	>3
Albumin - g/L	>35	28-35	<28
Prothrombin time (seconds)	<4	4-6	>6
Sum of Points	5-6	7-9	10-15
Stage	A	B	C
1-year survival rate (%)	95	80	44

Adapted from Pugh et al. (1973)[49]. Sometimes prothrombin index or international normalised ratio (INR) are used instead of prothrombin time[50].

SCREENING AND TREATMENT MODALITIES

Evidence suggests that patients with risk factors for hepatocellular carcinoma (especially decompensated cirrhotic patients) should undergo periodic screening. Several studies have shown that periodic screening of cirrhotic patients is cost-effective and increases survival[51]. However, the prognosis is dismal once a diagnosis of hepatocellular carcinoma is made as only a few cases are tractable to curative intervention[21]. In cases where it is impossible to operate, the tumour grows into the liver abhorrently producing local and distant metastasis (the bones and lungs are usual targets)[1]. For patients with advanced tumours evident by local and distant metastasis, death usually occurs in a mean time of 10 months, usually, a result of hepatic insufficiency, tumour cachexia, ruptured oesophageal or gastric varices, or, more rarely, haemoperitoneum due to rupture of a nodule[1].

The American Association for the Study of Liver Diseases recommends that patients with hepatitis B or cirrhotic nodules smaller than 1cm (as identified by ultrasonography) should be followed at three-month intervals, and the nodule should be considered a regenerative nodule if there is no evidence of further growth in two years; for patients with nodules greater than 1 cm, evaluation with contrast-enhanced CT or MRI is recommended to aid identification of cancerous nodules if present; once features typical of malignant transformation are identified, further screening is not required and a diagnosis of hepatocellular carcinoma is made; however, if contrast-enhanced CT or MRI fails to identify malignant features and a high index of suspicion remains, a second contrast-enhanced CT/MRI study or a histological investigation may be considered[21]. Some have suggested that the use of percutaneous needle biopsy be avoided as there is a small possibility (3%) of tumour spread in the needle path and the procedure also carries a risk of haemoperitoneum if nodule puncture occurs[52].

Ultrasonography is one method of screening that is cost-effective, widely available and provides an advantage of non-ionising radiation. The sensitivity of ultrasound for detecting hepatocellular carcinoma has been studied and is said to range from 60-80%[21]. However, its specificity is >90% for detection of the tumour in cirrhotic livers, thus making it the screening modality of choice in patients with hepatic cirrhosis[52]. Screening of patients with hepatic cirrhosis for hepatocellular carcinoma should be done twice a year (every six months), and some recommend that serum alpha-fetoprotein test also be carried out[21]. For alpha-fetoprotein, a value greater than 400ng/ml is highly suggestive of hepatocellular carcinoma; however, a value that exceeds 1000ng/ml is diagnostic.

MRI and/or contrast-enhanced abdominal CT is required for the definitive diagnosis of hepatocellular carcinoma. The sensitivity and specificity of MRI for detection of hepatocellular carcinoma is 81% and 85% respectively[21]. Although CT provides a sensitivity of only 68%, its specificity is more remarkable at 93%[53]. Of note, contrast enhancement improves the detection of malignant transformation. Contrast-enhanced CT and MRI scans will highlight a nodule (on a background of normal parenchyma) with remarkable enhancement in the arterial wash-in phase (where the nodule appears hypersensitive or hyperattenuating) as well as the late wash-out phases (where the nodule undergoes rapid elimination of the contrast and appears hypodense or hypoattenuating)[21].
In the event of a definitive diagnosis of hepatocellular carcinoma, a CT scan of the chest is recommended for staging[52]. If extrahepatic metastases are found, this contraindicates liver resection and transplantation[30].

PARTIAL HEPATIC RESECTION

The most effective treatments for hepatocellular carcinoma are liver resection and liver transplantation. Of note, for tumours smaller than 2cm, ablative therapies such as microwave ablation, radiofrequency ablation and percutaneous ethanol injection may have a small potential for cure[51]. However, these are reserved for high surgical risk patients (the elderly and patients with multiple comorbidities) in whom both liver resection and transplantation are contraindicated[21].

Ideal candidates for partial resection include non-cirrhotic patients with hepatocellular carcinoma[21]. The cirrhotic liver responds poorly to partial resections because of the decrease in regenerative capacity and function. Hence, for patients with cirrhosis, a thorough evaluation of liver function (using the Child-Pugh classification and evaluation of serum albumin, serum bilirubin, INR, ascites and encephalopathy) is required before a decision to resect is reached[52]. It is crucial to consider the quality of the remaining parenchyma before partial resection, as the hepatic functional reserve and the regenerative capacity of remaining parenchyma are significant determinants of risk of liver failure following partial resection[52]. Partial resection is contraindicated for patients with oesophageal varices, portal hypertension (with hepatic venous pressure gradient >10mmHg), thrombocytopenia (platelet count <100,000/mm^3 in cirrhotic patients is indicative of portal hypertension) and macrovascular invasion of branches of the portal veins or hepatic veins (evident by CT angiography)[6,21,52]. For non-cirrhotic patients, the minimum amount of parenchyma that should be maintained after partial resection ranges from 20-40% of the original volume[21], but this is not the case for cirrhotic patients in Child-Pugh class A who require preservation of a minimum of 50% of the initial hepatic volume[54]. The ideal surgical resection margin for HCC is 2cm[54]. Child-Pugh class C patients with decompensated cirrhosis are never suitable candidates for partial resections as it carries a high risk of liver failure and death in this class of patients. The choice curative option is limited to liver transplantation in these patients[21].

THE ROLE OF ADJUVANT THERAPY AFTER RESECTION

Of high importance is the treatment of underlying viral hepatitis following partial resection. There is much evidence supporting the use of the tyrosine kinase inhibitor, sorafenib, in the treatment of advanced hepatocellular carcinoma[55]. Nevertheless, randomised controlled trials have demonstrated little evidence supporting the use of sorafenib as adjuvant therapy following partial resection[56]. Antiviral drugs such as sofosbuvir, simeprevir, daclatasvir may achieve more than 90% efficacy in the treatment of hepatitis C[57].

The five-year recurrence of cancer following partial resection is greater than 70%; hence it is not uncommon to initiate chemotherapy after resection to target vestigial microscopic neoplastic cells[21]. If the decision to initiate chemotherapy following partial resection is to be made, this must be done with the most substantial available evidence to ensure clinical benefit and cost-effectiveness. In one meta-analysis done almost two decades ago which evaluated the effect of hepatic intra-arterial epirubicin followed by intravenous chemotherapy in a total of 108 patients enrolled in three randomised controlled clinical trials, it was found that chemotherapy yielded poor results when utilised as adjuvant treatment for hepatocellular carcinoma[58]. In another more recent meta-analysis which aimed to investigate the use of hepatic transarterial I-131 lipiodol for tumour chemoembolisation in 334 patients enrolled in two randomised clinical trials and three case-control studies, lipiodol demonstrated statistically significant benefit over the control group[59].

LIVER TRANSPLANTATION

It is worth noting that liver transplantation is only recommended in cirrhotic patients with hepatocellular carcinoma if there is no evidence of local nodal or distant metastasis. According to the Milan criteria, for patients without nodal or distal metastasis, liver transplantation may only be considered if there is a single tumour measuring 5cm or up to three tumours, each not exceeding 3cm[60]. The prognosis after transplantation for tumours greater than 5cm is abysmal. This is because tumours of this size are more likely to have infiltrated the vasculature microscopically[61]. Transplantation in such patients may present unnecessary risks without providing comparable benefit.

INTERVENTIONAL RADIOLOGY

For patients awaiting transplantation, several interventional radiology procedures are routinely employed in the temporary management of the disease[21]. Interventional radiology utilises procedures such as percutaneous ethanol injection, transarterial embolisation, transarterial chemoembolisation and radiofrequency ablation.

Both transarterial embolisation and transarterial chemoembolisation involve the injection of chemical agents into tumour vasculature intending to induce ischemic coagulative necrosis in the tumour. In transarterial embolisation, the embolising agent (commonly polyvinyl acetate or microspheres) is carefully injected into tumour vasculature via coaxial microcatheterism[21]. Transarterial chemoembolisation, on the other hand, involves the injection of lipiodol emulsified chemotherapy (commonly doxorubicin, mitomycin C and cisplatin or their cocktail) into the tumour vasculature and subsequent infusion of the same embolising agents used for transarterial embolization[21]. Response to embolisation treatment is monitored with contrast-enhanced intravenous CT. These embolisation techniques are particularly useful when there is more than one tumour nodule in a hepatic lobe[62].

Although commonly used for patients awaiting liver transplantation, these procedures are also employed as palliative treatment for patients that are not suitable candidates for partial resection or transplantation[21]. They are, however, contraindicated for patients in Child-Pugh Class C62. The goal of embolisation therapy is to obliterate every tumour. If tumour recurrence occurs, the embolisation therapy should be at intervals of 60 to 120 days[21]. Transarterial embolisation and transarterial chemoembolisation have yielded promising results in patients awaiting liver transplantation; tumour progression occurs in less than 10% of patients treated with embolisation therapy, and the five-year survival post-transplantation is almost 70%[62]. Another contraindication of transarterial embolisation and transarterial chemoembolisation is portal vein thrombosis. In such patients, radioembolisation via percutaneous transarterial injection of yttrium-90 microspheres, I-131 labelled lipiodol or rhenium-1888 into the tumour should be considered[21].

Percutaneous ablation techniques used in patients with hepatocellular carcinoma include radiofrequency ablation and chemical ablation (with ethanol or acetic acid). Radiofrequency ablation involves the heating of tumour at elevated temperatures, promoting thermal coagulation necrosis. This is done using imaging guidance but may also be done via laparoscopy or open surgery. Radiofrequency ablation is used safely for patients with tumours measuring up to 5cm awaiting transplantation and may yield survival rates and results comparable with resection for patients with BCLC stage 0 and A[51]. Radiofrequency ablation can also serve as palliative therapy and is the treatment of choice for the elderly and patients with comorbidities who are unsuitable candidates for resection[21]. In this cohort, it is advised that radiofrequency ablation be used in concert with other treatment modalities such as transarterial embolisation or transarterial chemoembolization[21] A caveat of radiofrequency ablation is that it is not to be performed if the tumour is in close proximity to major vessels or branches of the biliary tree. On the other end of the temperature spectrum, cryotherapy may be employed for tumours close to blood vessels. This involves the ultrasound-guided insertion of multiple ice probes (at -20°C) near the tumour, which cause necrosis[21].

Chemical ablation using ethanol involves the injection of ethanol into the tumour via image-guided percutaneous puncture[62]. The aim is also to induce necrosis in the tumour as ethanol enhances denaturation of structural and functional proteins and ultimately, cell death. Chemical percutaneous ablation using ethanol has produced significant results when the tumour is less than 3cm and has a more superficial location within the liver[62,63]. Moreover, it is very cost-effective and is suitable as palliative treatment for Child-Pugh class A and B patients who are not candidates for partial resection[62]. Acetic acid shows comparable results to ethanol when employed in chemical ablation techniques and is considered a suitable alternative[51].

It is worth mentioning that radiofrequency ablation has been shown to provide less risk of local recurrence, more extensive tumour necrosis and more prolonged survival when compared with chemical ablation. However, the evidence of survival benefit for radiofrequency ablation is only significant when the tumour is smaller than 2cm[63].

SORAFENIB

The expression of drug resistance genes such as glutathione-S-transferase and ABCB1, which codes for p-glycoprotein renders hepatocellular carcinomas resistant to most chemotherapy agents[21]. The tyrosine kinase inhibitor Sorafenib has, however, demonstrated considerable benefit in clinical trials. It is the first systemic treatment that demonstrated a survival benefit over placebo in two randomised controlled phase III clinical trials[64,65]. In one of the early trials, sorafenib showed a three-month survival benefit over the placebo group in patients with advanced hepatocellular carcinoma[66]. Sorafenib is currently considered standard therapy for patients with advanced hepatocellular carcinoma evident by symptoms of hepatic disease, vascular invasion and extra-hepatic

metastasis[37]. The Child-Pugh class of the patient is a significant indicator of prognosis and must be taken into account when treating advanced hepatocellular carcinoma with sorafenib[45]. Although most guidelines recommend sorafenib for advanced hepatocellular carcinoma with Child-Pugh class A, the use of sorafenib is still considered controversial for patients with Child-Pugh B primarily due to the lack of evidence from any prospective randomised controlled trials in such patients[37]. This is probably because trials on sorafenib have traditionally included patients with Child-Pugh class A almost exclusively in order to avoid the potential confounding of a treatment-related anti-tumour effect by death from underlying cirrhosis in patients in other Child-Pugh classes[55]. In one retrospective study of prognostic factors in patients with advanced hepatocellular carcinoma treated with sorafenib, it was found that plasma AST level at baseline (which is an indicator of ongoing hepatocellular damage) was a useful tool in identifying Child-Pugh class B patients who were more likely to benefit from sorafenib treatment[67]. Notably, the survival benefit provided by sorafenib may also result from the improvement of portal hypertensive syndrome and not just the anti-tumour effects alone[67,68].

However, there have been no randomised trials to study this additional beneficial effect. The results of sorafenib in patients with Child-Pugh class C have been rather dismal, and the current recommendations suggest only best supportive care for those who do not meet the criteria for transplantation[37].

TREATMENT OF THE UNDERLYING LIVER DISEASE

Evidence suggests that a significant number of patients with hepatocellular carcinoma do not die not from effects of the malignancy but rather from common complications of liver cirrhosis and portal hypertension such as variceal bleeding, renal failure and infections[69]. Therefore, patients with hepatocellular carcinoma would benefit from treatment of underlying liver disease in addition to effective anti-tumour treatment. In this regard, the management of patients with hepatocellular carcinoma should include evaluation and treatment of portal hypertension and varices[70].

Patients with malignant transformation following Hepatitis B induced cirrhosis are also to be considered for adjunct therapy as sustained hepatitis B viraemia is associated with an increased risk of recurrence of hepatocellular carcinoma after resection[71]. Several studies have shown that hepatitis B antiviral therapy results in favourable outcomes for candidates of liver resection [72-74].
Adjuvant treatment of hepatitis C is also associated with clinical benefit for hepatocellular carcinoma patients as one meta-analysis demonstrated prognostic improvement following interferon therapy for chronic hepatitis C virus after local ablation or surgery[75]. European guidelines recommend that all HBsAg-positive patients receive treatment with a potent nucleoside/nucleotide analogue that has a high threshold for resistance in order to achieve the lowest possible level of HBV DNA before transplantation to prevent recurrence[76]. Patients may also be treated with the same drugs after liver transplantation in combination with hepatitis B immunoglobulin to ensure an adequate reduction of risk of hepatitis B recurrence to less than 10%[76]. Interferon free treatment regimen is recommended for patients with hepatitis C awaiting liver transplantation or in whom recurrence of viraemia has occurred after transplantation[77]. Other modifiable risk factors such as alcohol should also be addressed with patients as it has been shown that sustained alcohol abuse is associated with poorer prognosis and reduced survival in patients with hepatocellular carcinoma while cessation reduced cancer-related mortality[78].

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