INTRODUCTION

Hepatocellular carcinoma (HCC) is a primary malignant tumour of the hepatocytes with a dismal prognosis. Median survival remains less than 1 year after diagnosis and the five-year survival rate of patients with HCC is below 10%. Survival can, however, be variable depending on the biological behaviour of the tumour (defined by the size, number, and vascular invasion) and the underlying liver function. In sub-Saharan Africa, HCC patients present to hospital with advanced disease which suggests that either the tumour variant in this region runs an aggressive course or there is delay in presentation. Liver transplantation remains the most effective treatment and offers the greatest hope of survival to patients with HCC. It provides the widest possible resection margins, removes the remaining liver that continues to be at high risk for developing new tumours and replaces the diseased liver. Unfortunately, however, there is hardly any centre in sub-Saharan Africa, including Nigeria, where liver transplantation is available. This guideline is therefore aimed at providing practitioners in this resource-constrained setting with the necessary information that can help detect liver cancer at an early stage when there is a possibility of cure and to enhance preventative measures.

Epidemiology

HCC accounts for over 90% of primary liver cancers and 7% of all cancers. Even though it is the fifth most common cancer in men and eight most common cancer in women (749,000 new cases/year), it is the third cause of cancer-related death (500,000 to 1 million deaths/year)\(^2\). Worldwide, the incidence of HCC peaks at the eighth decade of life (70-79 years) and has a male to female ratio of 2.4 to 1.0. Highest incidence rates occur in South-east Asia, sub-Saharan Africa and Melanesia; these areas account for 85% of cases\(^1\). Incidence rates are low in developed countries (crude incidence in European Union is 8.29/100,000) except in southern Europe\(^3\).

Worldwide, there is a growing incidence of HCC mainly due to hepatitis C virus (HCV)-related liver disease and an emerging liver disease like non-alcoholic fatty liver disease (NAFLD). In the US, for example, HCC death rates appear to have increased by more than 40% over the period of 1990 to 2004\(^5\). In countries that have applied universal infant immunization against hepatitis B virus (HBV), such as Taiwan, the incidence of HBV-related HCC has declined. Approximately 90% of HCC have known aetiological risk factors and these are (1) chronic viral hepatitis (types B & C), (2) alcohol, (3) dietary aflatoxin consumption, (4) α1-antitrypsin deficiency, (5) haemochromatosis, (6) NAFLD, (7) cigarette smoking and (8) human immunodeficiency virus (HIV) co-existing with chronic viral hepatitis\(^6,7\). In the developing world, 60% of HCC are due to HBV while the figure for the developed world is 20%, the majority being caused by HCV. HBV-related predictors of HCC development include HBeAg positivity, high viral load and HBV genotype C and HCV-related predictor
is genotype 1b. Any condition that leads to cirrhosis is an important risk factor for HCC. Overall, one-third of cirrhotic patients will develop HCC in their lifetime. Factors in cirrhotic patients that may suggest HCC development include platelet count <100,000/mm³, oesophageal varices, older age, male gender, elevated portal pressure and erythrocytosis.

**Current HCC Situation in Nigeria**

Nigeria belongs to the region of the world with a moderately high incidence for HCC (11-20/100,000). Middle-aged Nigerians in the 40-59 years age bracket are predominantly affected and the overall national male to female ratio is 3.7 : 1. The main aetiological agent for HCC is chronic infection with hepatitis B virus (HBV) and the national mean sero-prevalence rate for HBsAg among Nigerian HCC patients is 59.6%. The role of dietary aflatoxin consumption in hepatocarcinogenesis in Nigeria does not appear appreciable when compared with findings in other sub-Saharan African countries. With a national mean anti-HCV sero-prevalence rate of 11%, the implementation of universal immunization against HBV right from the time the hepatitis B vaccine became available in the mid-1980s has resulted in significant reduction in the incidence of HCC in some countries, e.g. Taiwan and Singapore. In 2001, the National Programme on Immunization (NPI) institutionalized HBV vaccine in Nigeria but it was not until late 2003 that the vaccine became fully integrated into the NPI. Actual immunization was started in all local government areas in 2004 with the aim of achieving 80% coverage by 2007. Unfortunately, data is not available on national immunization coverage and so it is not possible to confirm if this goal has been attained. From foregoing, therefore, it is obviously too early to comment on the impact of hepatitis B immunization on HCC incidence in Nigeria.

**Indications and Importance of HCC Surveillance**

Patients at high risk of developing HCC should be considered for and offered to be entered into a regular surveillance programme. This is aimed at early detection of HCC that provides the only opportunity for any beneficial treatment. Therefore, the rationale behind surveillance for HCC employing regular liver ultrasound scan and serum tumour marker measurement in asymptomatic but high risk patients is to enable the detection of early tumour that could be amenable to surgical treatment with curative intent. This is helpful in reducing disease-related mortality. HCC detected after the onset of symptoms has a very dismal prognosis which, unfortunately, is the case with most HCCs seen in Nigeria. HCC surveillance is generally recommended for the following patients and conditions:
Liver cirrhosis of any cause
HBsAg positive individuals (especially those who are HBeAg positive or have serum HBV DNA levels > 2,000 IU/ml)
- Africans above 20 years of age
- Asian males > 40 years
- Asian females > 50 years
Individuals with positive antibodies to HCV or increased serum HCV RNA
Positive family history of HCC
Significant alcohol consumption
Genetic haemochromatosis
Primary biliary cirrhosis
Elevated serum a-fetoprotein (AFP) (> 20ng/ml)

Surveillance Tests
The most widely used tools for HCC surveillance are AFP and liver ultrasound scan. Des-gamma-carboxy prothrombin (DCP) may be substituted for AFP while abdominal CT scan may be used in place of liver ultrasound. The recommended surveillance interval is 6 months and this is based on the estimated HCC doubling time.

AFP is a glycoprotein of 591 amino acids and a carbohydrate moiety synthesized by the liver and yolk sac during foetal development. It is the most abundant plasma protein found in the human foetus, thought to be the foetal form of serum albumin. Plasma levels of AFP decrease rapidly after birth but begin decreasing prenatally starting at the end of the first trimester. Normal adult levels are usually achieved by the age of 8 to 12 months. The normal adult range for serum AFP is 10-20ng/ml. Levels of > 400ng/ml are regarded as significant for HCC while levels of > 1,000ng/ml are diagnostic. However, rising serum AFP levels over time even if less than 400ng/ml could be diagnostic of HCC. AFP is the most widely studied and utilized tumour marker for HCC surveillance. One of the drawbacks to the use of AFP as a screening tool for HCC is the fact that 20% of HCC do not produce AFP even when very large. In addition, AFP can be secreted by regenerative liver cells in patients with benign liver diseases such as liver cirrhosis, chronic hepatitis, acute hepatitis and non-hepatic conditions like malignancies of the pancreas, testes and ovaries, hydatidiform mole, omphalocele, yolk sac tumour, neural tube defects, ataxia telangiectasia and non-seminomatous germ cell tumour. This makes AFP poorly specific for HCC.

Des-g-carboxy prothrombin (DCP) is an abnormal prothrombin molecule that arises from an acquired defect in the post-translational carboxylation of the prothrombin precursor in malignant cells. The same defect can be induced by vitamin K absence or antagonist and DCP has, therefore, also been called prothrombin induced by vitamin K absence (PIVKA). Its level is particularly increased in HCC. A serum DCP level of > 40 mAU/mL is usually regarded as significant while levels > 150 mAU/mL could be diagnostic. There have been conflicting reports on the superiority of DCP over AFP as a biomarker for HCC. On a general note, while AFP may be elevated in benign liver diseases, DCP is only produced by liver malignancy. Also, the sensitivity of these tumour markers depends on the tumour size as well as on their serum cutoff values. DCP is apparently more sensitive for larger tumours (> 3cm)29. In a US study, the sensitivity and specificity of DCP in diagnosing HCC were found to be 74% and 86% respectively while those for AFP were 61% and 81% respectively30. The latter study concluded that biomarkers are needed to complement ultrasound in the detection of early HCC. In a pioneering Nigerian study, DCP had a sensitivity and specificity of 98.5% each at a cutoff value of 140 mAU/mL and was found to be superior to AFP in differentiating HCC from benign liver disease31.

In general, individuals at the risk of developing HCC need to be entered into surveillance programme. Surveillance should be performed using 2-D abdominal ultrasound scan (USS) by experienced sonologists and AFP every 6 months. Shorter intervals of 3 to 4 months may be advisable for those with hepatic nodule < 1cm, patients with normal ultrasound and elevated serum AFP and those on follow-up after resection or loco-regional therapy. The sensitivity and specificity of USS in diagnosing HCC have been reported to be 58-89% and >90% respectively32,33. However, with early-stage HCC the sensitivity falls to 63% and ultrasound detection of HCC with cirrhotic background is usually difficult34. Accuracy of HCC detection by USS is therefore dependent on the
expertise and experience of the operator. The guidelines of both the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) recommend the use of USS only for HCC surveillance\textsuperscript{35,36}. The EASL does not recommend AFP for surveillance because it is claimed to have only 6-8% gain in HCC detection. Computerized tomography (CT) or Magnetic Resonance Imaging (MRI) scan may be used instead of USS in cases of obesity, chest wall deformity or intestinal gas.

**Recommendation for Nigeria**

1. The following individuals or patients at high risk of developing HCC should be entered into surveillance programmes.
   a. All HBsAg positive individuals over 20 years of age including chronic hepatitis B (CHB) patients in the inactive phase (i.e. HBeAg negative, anti-HBe positive, normal serum alanine aminotransferase (ALT), serum HBV DNA <2,000 IU/ml and normal liver histology or minimal/ mild necroinflammation without fibrosis)
   b. Individuals with positive antibodies to HCV or increased serum HCV RNA
   c. Patients with liver cirrhosis from any cause
   d. Individuals with a positive family history of HCC

2. The surveillance tests to be used should include serological and imaging investigations as follows:
   a. Serum a-fetoprotein (AFP) (Des-g-carboxy prothrombin (DCP) may be used in place of AFP if available and affordable)
   b. Real-time (2-D) abdominal USS (to be performed by trained and experienced personnel in tertiary health centres)

   **Both tests are to be done at the same time every 6 months**

**CONFIRMATION OF DIAGNOSIS**

**Imaging Techniques**

Once one or both surveillance tests become abnormal, the next step is to confirm the diagnosis of HCC. When a focal lesion is detected in the liver of a patient with cirrhosis and/or a significant elevation of serum biomarker occurs (AFP e” 200ng/ ml or DCP e” 40 mAU/ mL) during surveillance it becomes necessary to confirm diagnosis of malignant transformation. The initial diagnostic test is with triple-phase helical computed tomography (CT). The demonstration of arterial enhancement (hypervascularity) followed by hypointensity (washout) of the tumour in the portalvenous and delayed phases is diagnostic of HCC. If this sign is not demonstrated, a triple-phase, dynamic contrast-enhanced magnetic resonance imaging (MRI) may then be carried out. The latter imaging technique is better in the characterization and diagnosis of HCC. On the other hand, both techniques may be used concurrently for the confirmation of the diagnosis of HCC. When both tests are indicative (i.e. arterial hypervascularity plus venous or delayed washout), the diagnosis of HCC is confirmed. Also, a diagnosis of HCC can be confidently made if in a patient with cirrhosis a liver mass >2cm is demonstrated by CT or MRI with the typical features already mentioned.

**Liver Biopsy**

If there is a discrepancy between CT and MRI or the hepatic mass is 1-2cm in size or a focal hepatic mass is detected in a non-cirrhotic liver, a liver biopsy should be undertaken. A targeted biopsy (under US or CT guidance) should be employed in this setting. There is a risk of tumour seeding in the needle track although the risk is relatively low at 1-3%. In view of this risk, it has been advised that the biopsy of a potentially resectable lesion should be avoided\textsuperscript{37}. This risk of tumour seeding or even bleeding is, however, minimised if a 22-gauge needle is used for the biopsy. A diagnosis of HCC is readily confirmed by liver biopsy and it is often possible to confirm the existence of liver cirrhosis. An additional advantage is the possibility of determining the aetiology of the HCC, e.g. HBV DNA and HBcAg detection.

The macroscopic features of HCC depend on whether there is cirrhosis in the residual liver tissue. Up to two-thirds of cases seen in Nigeria have background liver cirrhosis and the tumour is multicentric affecting diverse portions of the liver either as synchronous tumours or as intrahepatic metastases. Invasion into blood vessels, especially the portal vein, is a distinctive attribute of HCC. Tumour emboli in the portal vein are present in more than 70% of autopsies of advanced...
cases. Intrahepatic metastasis is caused mostly by tumour spread through the portal vein. Spread into bile ducts is less common, only seen in less than 10% of autopsy cases. Extrahepatic metastasis is most commonly haematogenous and the lungs are the most common sites of the metastases. Lymphatic spread is also common but rarely affects distant sites. The common patterns of HCC seen in Nigerian patients are trabecular, pseudoacinar and, less commonly, the scirrhous patterns. The trabecular pattern is the commonest and it frequently occurs also in significant numbers of the pseudoacinar type as well. The fibrolamellar type, reputed to be of excellent prognosis, is extremely rare in Nigeria. The cytological grades of HCC are made into 3 grades, namely, well differentiated, moderately differentiated and poorly differentiated/undifferentiated subtypes. In multicentric neoplasms all the grades may be present in the various foci. This questions the value of tumour grading in the formulation for most of our patients. However, in unicentric tumours, the tumour grades are roughly correlated to the sizes of the tumours with those less 3cm being mainly of the well-differentiated grade and as such, with excellent prognosis if resection is carried out. Multicentric tumours are associated with a high rate of recurrence, even after curative resection, making treatment difficult and prognosis poor.

Interpretation of biopsies in early lesions can be challenging. Distinguishing between high-grade dysplastic nodules and HCC is usually difficult. Staining for glypican-3, heat shock protein 70 and glutamine synthetase may be necessary to differentiate the two lesions since positivity for two of these three stains confirms HCC\(^3\). A negative biopsy does not completely rule out malignancy and surveillance may be resumed albeit at a reduced frequency of 3 months for the next 2 years. A return to the standard 6-monthly follow-up is suggested after a 2-year cancer-free surveillance.

**Cytological Methods**

Since most of our HCC patients present late, they tend to be very ill and the clotting profile is usually deranged, biopsy is not advisable and cytological methods are to be resorted to in such situations.

**a. Ascitic fluid tap**

Ascitic fluid cytology is a cheap and quick way of diagnosing HCC in the appropriate clinical setting when the disease is being considered as a differential diagnosis of ascites. In capable hands, malignant liver cells are readily recognizable. They are usually in profuse numbers occurring singly and in large clusters. They are usually remarkably well preserved even in ascitic fluid that takes long to get to the laboratory. The cells are usually pink, polygonal or round and with centrally-placed nuclei and rarely show atypical mitoses. Regardless of their benign appearance, the presence of appreciable quantities of liver cells in ascitic fluid should raise a suspicion of liver malignancy.

**b. Fine needle aspiration of the liver**

The diagnostic yield of fine needle aspiration cytology (FNAC) of the liver in HCC patients may be improved by doing the aspiration under ultrasound guidance. There may be ambiguity in the appearances of the cell if the tumour is a well differentiated one or the aspirated space occupying lesion is a regenerative nodule.

**Recommendation for Nigeria**

1. Once a surveillance test (or both) becomes abnormal (for US, the nodule must be >1cm), an abdominal spiral CT examination should be done. Demonstration of arterial enhancement and venous or delayed phase washout in a liver nodule confirms HCC.
2. Contrast-enhanced MRI may be undertaken if the CT is equivocal or both tests may be done concurrently where the facilities exist and patient can afford the cost.
3. Targeted liver biopsy or fine needle aspiration should be carried out where there is discordance in the CT and MRI findings. Where both CT and MRI show the typical sign of HCC (i.e. arterial enhancement followed by venous or delayed phase washout), liver biopsy may be avoided.
4. If both CT and MRI fail to show the positive sign of HCC or if the liver biopsy/aspiration is negative for malignancy, HCC surveillance should be resumed for the patient. The frequency of surveillance should be 3 monthly for the first 2 years.

AFP, a-fetoprotein; DCP, des-g-carboxyprothrombin; USS, ultrasound scan; CT, computerized tomography; MRI, magnetic resonance imaging
HCC Staging Schemes (see Appendix)
Several staging and scoring systems for HCC have been developed. They include tumour, nodes & metastasis (TNM) classification, Child-Pugh classification, Performance Status Test (PST) & Karnofsky Index, Okuda staging system, Barcelona Clinic Liver Cancer (BCLC) staging system, Cancer of the Liver Italian Programme (CLIP), Chinese University Prognostic Index (CUPI), Japanese Integrated System (JIS)\textsuperscript{39}. Even though there is no worldwide consensus on the use of any of these staging schemes, the BCLC system is most favoured because it is the only system that relates staging to treatment indication (see fig. 2.). It also incorporates some of the other staging systems, e.g. Child-Pugh, PST and TNM.

Guidelines on Management of HCC

High Risk Group for HCC: Serum AFP or DCP every 6 months
Real-time abdominal USS every 6 months

USS detects a nodules or serum AFP/DCP becomes abnormal

Spiral CT/ MRI

Typical HCC image
Atypical HCC image
Discrepancy b/ w CT & MRI
No lesion

Tumor diameter >2cm?

No
Follow-up at interval of 3 months

No growth in size/
disappearance of tumour
Move to routine surveillance

Yes

Optional investigations
CT-angiography
Liver-specific contrast-enhanced MRI
Contrast USS
Targeted liver biopsy

Definitive diagnosis of HCC
No definitive diagnosis of HCC

Fig. 1: Surveillance and diagnostic algorithm for hepatocellular carcinoma (HCC) AFP, \(\alpha\)-fetoprotein; DCP, des-\(\gamma\)-carboxyprothrombin; USS, ultrasound scan; CT, computerized

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Recommendation for Nigeria

1. Once a diagnosis of HCC is made, an attempt should be made to stage the disease according to the BCLC staging system.

Treatment Modalities for HCC

In planning the treatment for HCC, it is important to constitute a multidisciplinary team that includes the hepatologist, surgical gastroenterologist, oncologist, radiologist and pathologist. The treatment of every patient with HCC should always be discussed and planned by this multidisciplinary team. Certain factors should be taken into consideration before initiating treatment in these patients. These factors include the presence or absence of liver cirrhosis, the extent of disease, growth pattern of the tumour, hepatic functional reserve of the patient and the patient's performance status (i.e. the PST). Treatment modalities for HCC include the following:

1. Partial hepatectomy (surgical resection of the liver)
2. Liver transplantation
3. Local ablative therapy
4. Trans-arterial chemoembolization
5. Radiation therapy
6. Systemic chemotherapy

Partial Hepatectomy

Surgery remains the mainstay of HCC treatment and early diagnosis is the key to successful surgical intervention. Liver resection is the first-line therapeutic option for patients with localized tumours in the non-cirrhotic liver. These are patients with solitary tumours with well preserved liver function [i.e. normal serum bilirubin with either hepatic venous pressure gradient (HVPG) ≤ 10mmHg or platelet count ≥ 100,000/mm³] in the absence of vascular invasion. The suitability for resection is often based on the Milan criteria, namely, one nodule < 5cm or three nodules each ≤ 3cm. Five-year survival rates ranging between 30% and 90% have been obtained for resectable HCC. Higher 5-year survival rates of ≥ 70% have been obtained in patients with preserved hepatic function without portal hypertension whereas the presence of portal hypertension with or without hyperbilirubinaemia reduces survival rates to 25-50%. Resectability is favoured by certain tumour characteristics such as small tumour size, well differentiated tumour especially the fibrolamellar variant, unifocal tumour, lack of vascular invasion and the absence of cirrhosis in the unaffected portion of the liver. Resection has been limited primarily by low resectability rates and recurrent disease. Appropriate evaluation of patients, sometimes involving the use of pre-operative laparoscopic inspection, is crucial in order to enhance the chances of survival and prevent tumour recurrence. Worldwide, HCC patients diagnosed at early stages represent only < 40% of the patients. In Africa, the overwhelming majority (> 90%) of cases are advanced at presentation, thereby limiting the prospects of using surgical resection as a treatment modality.

Anatomic resections are recommended. Anatomic resections aiming at 2cm tumour-free margins provide better survival outcome than narrow resection margins <1cm and are recommended provided that the maintenance of appropriate function of the remnant liver volume is ensured. Tumour recurrence represents the major complication of resection and the pattern of recurrence determines the subsequent therapy allocation. In the case of recurrence, the patient is re-assessed with the BCLC staging system and re-treated accordingly. Patients with multi-focal tumours meeting Milan criteria with mild portal hypertension are not suitable for resection.

Liver Transplantation

Liver transplantation (LT) is considered to be the treatment option for patients who fulfil the Milan criteria (one tumour less than 5cm or up to three tumours none more than 3cm) but not suitable for resection. Patients who meet the expanded University of California San Francisco criteria (UCSF criteria: single tumour ≤ 6.5cm; two or three tumours, none >4.5cm; or total tumour diameter of ≤ 8cm; no vascular invasion) can also be treated with LT. A 3-year survival rate of 88% has been obtained with the application of the UCSF criteria for LT. Generally, a 5-year survival rate of 70% has been obtained with LT which is comparable to those of patients who undergo LT for end-stage liver disease without HCC. Peri-operative mortality and one-year mortality are expected to be approximately 3% and ≤10% respectively. Tumour recurrence occurs in 15% of cases and affects mainly the liver, lungs and bones.

There are two types of LT, namely, cadaveric liver transplantation (CLT) and live donor liver transplantation (LDLT). The LDLT requires a healthy
donor to give either the right or left hepatic lobe. There is, however, a donor mortality risk of 0.5%. The main limitation for LT is scarcity of livers. Loco-regional treatments such as percutaneous ablation or chemoembolization may be used when liver waiting time exceeds 6 months.

Local Ablative Therapy

Destruction or ablation of tumour cells can be achieved by the injection of chemical substances under US or CT guidance. Substances that have been used in this regard include 98% or 99.5% ethanol, acetic acid and hot saline. Alternatively, intra-tumoral insertion of a probe that modifies local tumour temperature [e.g. radiofrequency ablation (RFA), microwave, laser or cryotherapy with liquid nitrogen] may be used as local therapeutic modalities. Apart from US or CT assistance, these local ablative measures may also be carried out during laparoscopy. The indications are BCLC stages 0 to A tumours not suitable for resection and tumours less than 2cm in BCLC stage 0.

Percutaneous ethanol injection (PEI) requires that the patient be given 2-12ml of the ethanol twice weekly for 3 to 15 sessions on an outpatient basis. Complete tumour necrosis occurs in 90-100% of tumours less than 2cm. Local pain, fever and elevation of serum transaminases are some of the side effects patients experience with PEI.

RFA is the delivery of radiofrequency thermal energy to the HCC lesion leading to the necrosis of the tumour. During the procedure, a high frequency alternating current is delivered from the tip of an electrode and ions within the tissue attempt to follow the direction of the alternating current resulting in friction and eventual heating of the tissue. When the tissue temperature rises above 60°C, the tumour cells begin to die resulting in an area of tumour necrosis. RFA is recommended for tumour nodules with a maximum diameter of 5cm and that are not more than 3 in number. A 100% tumour necrosis must occur before RFA can be considered effective. RFA is often used as a palliative and as a bridge to LT. Where RFA is not technically feasible, PEI may be undertaken. RFA is contraindicated in tumours close to main biliary tree, abdominal organs and the heart. Five-year survival rates of >50% have been obtained with local ablative therapies in patients in Child-Pugh class A. Even though RFA is well tolerated complications may follow the procedure and these include fever, pain, bleeding, pleural effusion, haematoma and elevated serum transaminases.

Transarterial Chemoembolization

Transarterial chemoembolization (TACE) involves the intra-arterial (via the hepatic artery) injection of cytotoxic drug combinations such as doxorubicin and/or cisplatin and/or mitomycin, followed by lipiodol injection, gelfoam for vessel occlusion and degradable microspheres. It must be ensured that the portal vein is patent. TACE is recommended as a palliative technique for patients in BCLC stage B with multinodular asymptomatic tumours without vascular invasion or extra-hepatic spread. It is also indicated for downgrading patients whose tumours exceed the criteria for LT or to achieve local tumour control for those who meet LT criteria but who may have to be on the waiting list for more than 6 months. TACE has been shown to achieve partial responses in 15-55% of patients, and significantly delays tumour progression and microvascular invasion. Contraindications to TACE include Child-Pugh class C cirrhosis, multifocal bilobar tumour spread, presence of extrahepatic metastases, portal vein thrombosis and arterio-portal fistula.

Radiation Therapy

Radioembolization or selective internal radiotherapy is defined as the infusion of radioactive substances such as Iodine-131 (131I)-labelled lipiodol or microspheres containing Yttrium-90 (Y90) or similar agents into the hepatic artery. It is a non-surgical treatment modality for inoperable HCC that allows internal radiation therapy to be delivered directly to the tumour. Given the hypervascularity of HCC, intra-arterially injected microspheres will be preferentially delivered to the tumour-bearing area and selectively emit high-energy, low-penetration radiation to the tumour. This technique produces excellent necrosis and tumour responses. Unlike TACE, arterial embolization and ischaemia are not necessary for the therapeutic effect of radioembolization.

Radioembolization may therefore be performed for patients with portal vein thrombosis. It may serve as a bridge before other treatment modalities such as partial hepatectomy and LT or as a main therapy for patients with diffuse intrahepatic tumour spread. It may also be an alternative to TACE for those with
contraindications for TACE. The use of Y90 microspheres has the advantage of being able to treat all intrahepatic HCC lesions, including those that were originally undetected.

**Systemic Chemotherapy**

Systemic chemotherapy is the mainstay of treatment for patients with advanced HCC (i.e. BCLC stage C). These are patients who are not candidates for surgical resection, LT or loco-regional therapies. Unfortunately, however, HCC is relatively chemotherapy-resistant and several chemotherapeutic agents used have produced unsatisfactory results. Examples of agents used include doxorubicin, epirubicin (anthracycline derivatives), 5-fluorouracil, tamoxifen, octreotide, a-interferon, cisplatin and mitozantrone. They have given less than 10% objective response rates and no survival benefit. A combination of two or more of these agents has been tried but it produced significant treatment-related toxicity.

On November 16, 2007, the US Food and Drug Administration (FDA) approved sorafenib for the treatment of patients with unresectable HCC. Approval was based on the results of the SHARP (Sorafenib Hepatocarcinoma Assessment Randomized Protocol) study, an international, multicenter, randomized, double-blind, placebo-controlled trial in 602 patients with unresectable, biopsy-proven HCC. The trial was stopped after a pre-specified second interim analysis for survival revealed that sorafenib extended overall survival by 44% (HR=0.69; P = 0.0006) compared to placebo. Separate analysis demonstrated a statistically significant improvement in time to tumour progression in the sorafenib arm (median 5.5 vs. 2.8 months; HR=0.58, P = 0.000007)

Sorafenib has therefore emerged as the first effective systemic treatment for HCC after 30 years of research and is currently the standard-of-care for patients with advanced HCC (BCLC stage C). It is also indicated in those patients with tumours progressing upon loco-regional therapies.

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Sorafenib is a small multikinase inhibitor molecule that targets vascular endothelial growth factor receptor; platelet-derived growth factor receptor and Raf. It inhibits cell proliferation and angiogenesis and increases apoptosis in tumours. The dose of sorafenib is 400mg bid and it is administered orally. Side effects are mild to moderate in severity and include diarrhoea, weight loss, hand-foot skin reaction, alopecia, anorexia, voice changes and hypophosphataemia.

HCC patients in BCLC stage D have terminal disease and are to be offered the best supportive care available.

**Recommendation for Nigeria**

1. If tumour nodule fulfils Milan Criteria and there is no co-existing cirrhosis, patient should be offered surgical resection (partial hepatectomy)
2. If tumour nodule fulfils Milan criteria and there is only Child-Pugh class A cirrhosis, patient should be offered resection in a centre with experience with liver resection and liver supportive care
3. If tumour nodule fulfils Milan criteria and there is co-existing Child-Pugh class B or C cirrhosis, patient should be referred for orthotopic liver transplantation (OLT) abroad. In Nigeria presently, capacity building in hepatic resection and liver transplantation are still being developed.
4. If tumour nodule fulfils Milan criteria but there is co-morbidity or hyperbilirubinemia or increased portal venous pressure or, if for any reason, the tumour is not suitable for resection, patient should be offered a local ablative therapy. The type to be employed will depend on availability, expertise and cost.
5. If tumour nodule does not fulfil Milan criteria but fulfils UCSF criteria, local ablative therapy may be offered and then refer patient for OLT once tumour is downgraded.
6. If the tumour node fulfils neither the Milan nor the UCSF criteria and there is no vascular invasion, patient may be referred to any centre in the country that offers trans-arterial chemoembolization (TACE)
7. Patients presenting in the BCLC stage C may be offered sorafenib. This drug is currently available in the Nigerian market and may have to be sourced from representatives of the manufacturing company.
8. Patients presenting in the BCLC stage D should be offered the best available supportive, symptomatic care and made to
be as comfortable and pain-free as possible. Attention should also be paid to nutrition and psychological support.

Prevention of HCC

From a global perspective, prevention of HCC is of public health importance. This is more so because developing countries like Nigeria with a high burden of HCC have the least capacity and technological ability to manage the condition. In Nigeria, as in other sub-Saharan African countries, LT is not yet available and capacity for liver resection is poorly developed. The most cost-effective HCC prevention strategy is primary prevention of viral hepatitis B and C. Prevention of alcohol abuse and metabolic syndrome are also relevant. Another important preventive strategy for HCC is reduction of aflatoxin contamination of food through proper care of crops and food storage and preservation. There is a great need to increase HBV and HCV awareness among the health-care community in order to promote surveillance of patients who are at risk and achieve earlier diagnosis.

PRIMARY PREVENTION

General recommendations

1. Health education on viral hepatitis (to general population and health care providers; to take advantage of the annual World Hepatitis Day for this campaign)
2. Education on alcohol use/abuse and prevention
3. Food storage strategies to prevent aflatoxin contamination (e.g. through refrigeration)
4. Public health education on the dangers of obesity and the metabolic syndrome

Prevention of new infections

1. Improvement in medical care facilities to prevent infections, e.g. promotion of the use of disposable syringes and needles and avoidance of multiple-dose vials.
2. Promotion of safer trado-medical and cultural practices such as scarifications, tattooing, tribal marks, male circumcision and ear piercing by advocating the use of sterile and, if possible, disposable sharp instruments.
3. Practice universal precautions in both formal and informal health care facilities, e.g. safe disposal of sharps to avoid nosocomial infections through needle-stick and sharps injuries.
4. Universal infant immunization with the hepatitis B vaccine
5. Post-exposure prophylaxis against hepatitis B using the hepatitis B immunoglobulin (HBIG) and HB vaccination for health care workers and children born to HBsAg positive mothers

TREATMENT OF EXISTING HEPATITIS INFECTION

1. Treatment of patients with chronic hepatitis B
2. Treatment of patients with chronic hepatitis C

SECONDARY PREVENTION

See section on HCC surveillance

Recommendation for Nigeria

1. Universal infant immunization with hepatitis B vaccine is already incorporated into the National Programme on Immunization (NPI). However, there is a need to ensure that there is constant availability of the vaccine and 100% coverage for the country.
2. Immunization of HBsAg negative and, preferably also, anti-HBs negative high risk individuals such as medical & nursing students, health care personnel, law enforcement agents, military & para-military personnel and paramedics with HB vaccine.
3. Routine screening of prospective blood & organ donors and pregnant women for HBsAg and anti-HCV.
4. HCC surveillance for high risk persons with serial AFP and USS or CT scan.
5. Antiviral chemotherapy for all those with chronic hepatitis B or C eligible for treatment
6. HBsAg or anti-HCV positive persons to avoid alcohol and herbal remedies.
7. Passive immunization of babies born to HBsAg positive mothers with HBIG within 12 hours of delivery followed by active immunization.

Treatment of HBsAg positive pregnant women with very high viral DNA (e$10^6$ IU/ml) in the third trimester with oral nucleos(t)ide analogues to reduce the chances of maternofoetal transmission of HBV.
APPENDIX
A total score of 5-6 is considered class A (well-compensated disease), 7-9 is class B (significant functional compromise) and 10-15 is grade C (decompensated disease); INR, international normalized ratio.

**Table 1: Child-Pugh Classification**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Albumin, g/ dl</td>
<td>&gt;3.5</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
</tr>
<tr>
<td>Bilirubin, mg/ dl</td>
<td>£2</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>Seconds over control</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.8</td>
</tr>
</tbody>
</table>

**Table 2. Chinese University Prognostic Index (CUPI)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNM stage</td>
<td></td>
</tr>
<tr>
<td>I and II</td>
<td>-3</td>
</tr>
<tr>
<td>IIa and IIIb</td>
<td>-1</td>
</tr>
<tr>
<td>IVa and IVb</td>
<td>0</td>
</tr>
<tr>
<td>Asymptomatic disease</td>
<td>-4</td>
</tr>
<tr>
<td>Ascites</td>
<td>3</td>
</tr>
<tr>
<td>AFP &gt; 500 ng/ dL</td>
<td>2</td>
</tr>
<tr>
<td>Bilirubin</td>
<td></td>
</tr>
<tr>
<td>&lt;34 µmol/ L</td>
<td>0</td>
</tr>
<tr>
<td>34-51 µmol/ L</td>
<td>3</td>
</tr>
<tr>
<td>e&quot;52 µmol/ L</td>
<td>4</td>
</tr>
<tr>
<td>Alkalinephosphatase</td>
<td></td>
</tr>
<tr>
<td>e&quot; 200 IU/ L</td>
<td>3</td>
</tr>
</tbody>
</table>

Scores range between -7 and 12; AFP, a-fetoprotein; TNM, tumour, nodes.
Table 3: Cancer of the Liver Italian Program (CLIP)

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh class</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Tumor morphology</td>
<td>Uninodular</td>
<td>Multinodular</td>
<td>Massive OR</td>
</tr>
<tr>
<td></td>
<td>&lt;50% of liver volume</td>
<td>&lt;50% of liver volume</td>
<td>&gt;50% of liver volume</td>
</tr>
<tr>
<td>AFP (ng/ mL)</td>
<td>&lt; 400</td>
<td>≥ 400</td>
<td>-</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
</tr>
</tbody>
</table>

Score ranges from 0 to 6; AFP, a-fetoprotein

Table 4: Okuda staging system

<table>
<thead>
<tr>
<th>Points</th>
<th>0</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour size</td>
<td>&lt;50% of liver</td>
<td>&gt;50% of liver</td>
</tr>
<tr>
<td>Ascites</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Albumin (g/ dl)</td>
<td>&lt;3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Bilirubin (mg/ dl)</td>
<td>&lt;3</td>
<td>3</td>
</tr>
</tbody>
</table>

Okuda stage I, 0 points; Okuda stage II, 1 or 2 points; Okuda stage III, 3 or 4 points

Table 5: Performance Status (PST) and Karnofski Index

<table>
<thead>
<tr>
<th>Performance status</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No cancer-related symptoms. Normal lifestyle</td>
</tr>
<tr>
<td>1</td>
<td>Minor symptoms related to cancer. Capable of non-strenuous activity. Fully ambulatory</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Confined to bed or chair less than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Karnofski index</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>Normal. No symptoms, no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor symptoms</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; symptoms present</td>
</tr>
<tr>
<td>70</td>
<td>Capable of self-care but unable to carry on normal activities</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalized but death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; active supportive care needed</td>
</tr>
<tr>
<td>10</td>
<td>Moribund, rapid deterioration</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

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Table 6: Japanese Integrated System (JIS)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Child-Pugh</td>
<td>A</td>
</tr>
<tr>
<td>TNM by LCSGJ</td>
<td>I</td>
</tr>
</tbody>
</table>

Score ranges from 0 to 5; TNM, tumour; nodes, and metastasis; LCSGJ, Liver Cancer Study Group of Japan (see Table 8)

Table 7: TNM staging criteria for hepatocellular carcinoma (HCC)

- **T1** Solitary tumour without vascular invasion
- **T2** Solitary tumour with vascular invasion or multiple tumours none >5cm
- **T3** Multiple tumours >5cm or tumour involving a major branch of the portal or hepatic vein(s)
- **T4** Tumour(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

- **N0** Indicates no nodal involvement
- **N1** Indicates regional nodal involvement
- **M0** Indicates no distant metastasis
- **M1** Indicates no distant metastasis present beyond the liver

Stage grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>T factor</th>
<th>N factor</th>
<th>M factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1 + N0 + M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>T2 + N0 + M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>T3 + N0 + M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>T4 + N0 + M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIC</td>
<td>TX (any T) + N1 + M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>TX + NX (any N) + M1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 8: TNM staging according to the Liver Cancer Study Group of Japan (LCSGJ)

- **T1** Fulfilling 3 factors
- **T2** Fulfilling 2 factors
- **T3** Fulfilling 1 factor
- **T4** Fulfilling 0 factor

<table>
<thead>
<tr>
<th>Stage</th>
<th>T factor</th>
<th>N factor</th>
<th>M factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IV-A</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>OR</td>
<td>TX (any T)</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IV-B</td>
<td>TX NX (any N)</td>
<td>M1</td>
<td></td>
</tr>
</tbody>
</table>
REFERENCES