

REVIEW ARTICLE**HEPATOCELLULAR CARCINOMA: TIME FOR ACTION?****Archampong E.Q¹, Nkrumah KN², Darko R¹, Archampong TNA²**¹Department of Surgery, ²Department of Medicine, Korle Bu Teaching Hospital, Accra, Ghana**Introduction**

Hepatocellular carcinoma is the commonest primary cancer of the liver^{1,2}. Its incidence is increasing; indeed it has become the fifth commonest malignancy worldwide and the third leading cause of cancer-related death, exceeded only by cancers of bronchus and stomach. The incidence is extremely variable, with higher preponderance in East Asia and sub Saharan Africa, reflecting the prevalence of predisposing hepatopathies in these regions. However, of late the incidence has been rising in some Western countries, linked to epidemiological changes such as rising levels of adult-onset diabetes and the metabolic syndrome. Sub-Saharan Africa has long been noted for high incidence rates, however information has been surprisingly sparse, a reflection of the declining state of cancer registries in this region³.

In Ghana a national cancer registry is yet to take root, although regional centres have been accumulating data which have remained largely unpublished; this for the commonest cancer in the country. Advanced cases continue to report in the clinics for whom very little can be done, with the danger of clinical tolerance to these teeming numbers. As in several African countries Hepatitis B vaccination has been part of the national immunization programme for some time (≈5 years). It started in Ghana in 2008 for children under 5. Urbanization is proceeding at an advancing pace, obesity and other life-style ailments are on the increase, all on a background of a persistent HIV menace. These are factors that might clearly influence incidence of hepatocellular cancer in our populations. This article comes as a response to this threat, reviewing the epidemiology, level of surveillance, diagnosis and management of hepatocellular cancer with respect to the African Region.

Author for Correspondence:
Emeritus Professor E. Q. Archampong
University of Ghana
College of Health Sciences
Conflict of interest: None declared

Epidemiology

This does not only reflect the incidence and prevalence pattern of the disease but most importantly, holds leading clues to aetiology. It is estimated that 500,000 to one million new cases of hepatocellular Cancer occur annually with some 600,000 deaths; the closeness of the incidence and annual mortality indicates the dire outcome of the disease. The incidence rates are extremely variable, with areas of very high incidence (in excess of 20 per 100,000 population)- notable among these are Mongolia (99 per 100,000), Korea (49/100,000), China^{1,4} (35/100,000), Hong Kong and Thailand, sub-Saharan Africa (more than 10 cases per 100,000 population)- West Africa (Sene-Gambia) and South-East Africa-(Mozambique). There is an intermediate risk region (about 3-5 cases per 100,000 population) which includes Denmark, Italy and Latin America. A relatively low incidence (less than 3 cases 100,000 population) is seen in much of Western Europe, United States, Canada and Scandinavia. Even in this category of countries gradual increase in incidence of the disease has been noted in recent years, associated with upsurge of obesity, diabetes and the metabolic syndrome,^{5,1} and migration from areas with higher prevalence of the disease.

There are notable demographic trends: the disease has a predilection for males in whom the outcome of treatment and prognosis is poorer. The disease occurs at a younger age in the high incidence areas (30-40 years), whereas in North America the highest prevalence is among those aged over 65 years⁶. It is a matter of concern that while epidemiological data builds up rapidly in the low incidence countries which are experiencing a gradual rise in frequency of the disease, much less information is emanating from the high incidence countries in sub Saharan Africa over the past two decades. This contrasts with the trends for the East Asian high incidence areas, which have been reporting declining hepatocellular cancer rates, linked to nationwide hepatitis B vaccination⁷. In Africa although several countries have recently initiated hepatitis B vaccination as part of national immunization programmes, it is too soon for its influence to be reflected on the incidence rates.

What is worse, there is little evidence of monitoring to detect any such welcome change.

In Ghana the rates remain high – some 300 cases are seen annually in one Teaching hospital alone, generally presenting as advanced cases. (Tables 1 and 2). It is particularly important to stimulate activity in the cancer registries of several decades standing in West and South-Eastern sub Saharan Africa, to indicate the current epidemiological pattern of the disease in this region.

Table 1: HCC Patients seen at the Gastroenterology Clinic KBTH (2012-2013)

AGE RANGE	MALE	FEMALE	TOTAL
20-30	7	2	9
31-40	15	6	21
41-50	7	5	12
51-60	12	6	18
61-70	10	3	13
Over 70	1	1	3
TOTAL	51	23	74

- Male: Female Ratio 2.2:1
- Total attendance (2012-2013): 605
- Prevalence of HCC among gastroenterology/Hepatology patients: 10.6%

Table 2: Relative Mortality Statistics for HCC in the Department of Medicine, KBTH (7 Months)

	2012	2013
Total Admissions	3467	3398
Duration (Months)	7	6
Total Deaths	367	531
Hcc Deaths	28	21
Hepatitis B-Related Hcc	18(64.3%)	15(71.4%)
% Of Hcc Of Admissions	0.8	0.6%
% Of Hcc Of Deaths	7.6%	4.0%
Hcc Admissions/Month	4	3.5

Risk Factors

The major risk factor for the development of hepatocellular cancer is cirrhosis of the liver; however in both high and low incidence areas a significant number of presenting cases show no readily identifiable predisposing risk factors. The major known risk factors for these include viral (chronic hepatitis B and C), toxic (alcohol and aflatoxins), metabolic (obesity, diabetes and non-alcoholic fatty liver disease, hereditary haemochromatosis) and immune-related (primary biliary cirrhosis and autoimmune hepatitis)⁸. The geographical heterogeneity in the incidence of HCC is being strongly attributed to changing distribution and natural history of Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infections⁹.

Hepatitis B Virus (HBV)

A number of studies has confirmed the HCC risk of HBV infection especially in East Asian countries where most patients acquired the HBV as newborn infants^{10,11}. In this area the incidence of HCC in HBV-related cirrhosis is reported at 2.7%, and the probability of HCC transformation seems proportionate to the underlying liver disease. In sub Saharan Africa, HBV is endemic, mother to child (vertical) as well as community acquired (horizontal) transmission being common and the attributable fraction of HCC due to HBV rather high (circa 60%)¹². The impressive evidence favouring causal association of HBV and HCC led both International Agency for Research in Cancer (IARC) and WHO to classify HBV as a human carcinogen second only to tobacco¹³. Extensive studies of mechanisms of carcinogenesis in HBV infection suggest both host response factors through cirrhosis and viral factors through encoding of oncogenic proteins with multi-functional regulator gene transcription. The specific mechanism remains to be proven but appears increasingly through depression of the tumour suppressor p53 protein¹⁴. Through the close causal relationship of HCC and HBV, HCC has become the first human cancer amenable to prevention using mass vaccination programmes. Thus the burden of chronic HBV infection is expected to decline over many years from increasing utilization of HBV immunization¹⁵. The effect of this is yet to be experienced in sub Saharan Africa.

Hepatitis C Virus (HCV)

The strongest evidence for a causal link between HCV and HCC came from Okuda¹⁶ of Japan who hypothesized that a non-A or B (NANB) virus caused a significant proportion of HCC in Japan. It is now known to be the most important risk factor of HCC in

Western Europe and North America where epidemiological studies have shown up to 70% of patients with HCC have anti-HCV antibody in the serum. However African and Asian countries report lower though rising rates^{17,18}. Egypt has the highest prevalence of HCV in the world and this has been attributed to previous public health eradication schemes for schistosomiasis.

In contrast to HBV infection, older age (over 40years) is associated with increased risk of HCC. The rate of fibrotic progression in HCV infection and eventual HCC transformation is also influenced by male sex, HCV genotype and alcohol consumption. There is evidence that combined HCV and HBV infections carry a higher risk of developing HCC than infections with either virus alone. It has been estimated that the cumulative risk of developing HCC was 10%, 21% and 23% respectively after 5 years; and then 16%, 28% and 45%, after 10years⁴. Combined HCV and HBV infections are similarly associated with higher HCC transformation and at an earlier stage and age¹⁹. Furthermore co-infection with HIV is a frequent occurrence because of shared routes of transmission, and increased rates of HCC transformation have been reported²⁰.

Aflatoxin (AFB1)

This is a mycotoxin elaborated by fungi of the *Aspergillus* genus, frequently encountered in Asia and sub Saharan Africa where climatic conditions and storage techniques favour its contamination of grain, peanuts and legumes. Of the four genetically distinct forms AFB1 is found to be most widely distributed in areas with high HCC prevalence. These areas also coincide with the areas of high HBV endemicity, with the implication that AFB1 facilitates establishment of the HBV infection and also enhances the HCC transformation²¹. The latter is considered most likely to occur through somatic mutations of the tumour suppressor p53 gene²². Pesticides which are commonly used by peasant farmers, usually males, are presumed to produce similar mutagenic effects on hepatocytes that harbour HBV and HCV.

Alcohol, Tobacco and other Factors

The IARC accepted in 1988 that there is a causal relationship between alcohol consumption and HCC²³. However the underlying mechanism is far from clear. Earlier studies found alcohol a more significant risk factor in low incidence areas than in high incidence areas. This may have been due to lower mean alcohol consumption in high risk areas and/or due to dominant effect of chronic HBV infection masking any additional risk of alcohol consumption; recent studies have reported little difference in risk imposed by alcohol and HCV in comparison with alcohol and

HBV²⁴. It is certain that alcohol induces cirrhosis which is a factor in 60-90% of HCCs. The HCC transformation may be influenced by release of acetaldehyde and free radicals during ethanol metabolism.

The association between HCC and cigarette smoking remains tenuous, although some studies have indicated that the tobacco effect is limited to subsets of the population studies defined by HBV, HCV and genetic status. Some relationship between oral contraceptive use and benign hepatic adenoma has been known for some time and the question has been raised whether this extends to HCC. The evidence from case control studies suggests that the risk attributable to oral contraceptive use is limited in the absence of viral infections. The male preponderance of HCC raises the question of the role of endogenous hormones in the aetiology of this cancer. Studies have shown significantly increased blood testosterone levels in men with HCC who are chronically infected with HBV²⁵.

Diabetes Mellitus

Population – based studies in low incidence countries in Europe and North-America have shown diabetes mellitus as an independent risk factor for HCC, regardless of concomitant chronic HBV or HCV infection or cirrhosis of the liver. A two to three fold increase in HCC risk was demonstrated, with more than 60% of subjects showing no evidence of the commonly recognized risk factors²⁶. Similar observations have emanated from Japan, a high incidence region but none so far from sub-Saharan Africa. Again in low incidence countries, particularly USA²⁷, as part of the metabolic syndrome, obesity has emerged as a significant HCC risk in both men and women without diabetes. These studies need to be carried out in HCC high incidence areas.

Diet

Studies on dietary influence as risk factor for HCC have yielded conflicting results. Earlier reports of protective effects of diets high in milk, wheat, soya food, vegetables and fruits have not been confirmed. The weight of combined evidence from Japan and the US has led the World Cancer Research Fund and the American Institute of Cancer Research to conclude that diets high in vegetables reduce the risk of HCC²⁸.

Pathology

The morphological manifestations of HCC are extremely variable, being determined by the presence or absence and pattern of cirrhosis, as well as other changes that precede the genesis of the neoplasm. In high incidence areas of Asia and sub Saharan Africa where association with cirrhosis is extremely high (over 80%), three gross morphological forms are

encountered: (i) Nodular pattern, mimicking the pattern of the cirrhotic liver. This is the commonest pattern, accounting for 78%. (ii) Massive form, in which the tumour is more localized and may appear encapsulated. It may involve a whole lobe or part thereof (7%). (iii) Diffuse form (15%) where the entire liver is permeated by the tumour and is often seen in patients with micronodular cirrhosis. The last mentioned is the least amenable to surgical resection.

Three histological patterns are discernible. (i) Microtrabecular form with almost normal looking hepatocytes, where diagnosis depends on the overall growth pattern of the tumour. (ii) Vesicular form with tendency of tumour cells to form acini. (iii) Atypical or anaplastic form with multinucleated giant cells. Combinations of the three patterns occur and are often mixed with columnar cells akin to cholangiocarcinoma.

Clinical Features And Diagnosis

In high incidence areas such as sub Saharan Africa presentation is invariably late and clinical features leave little doubt about the diagnosis. The classic presentation takes several forms:

- Persistent right upper quadrant pain, tender hepatomegaly, with general deterioration in health, anorexia, weight loss progressive cachexia in a person under surveillance for cirrhosis. Tender nodular hepatomegaly in this setting is highly suggestive of malignant transformation. A bruit or friction rub is heard over the liver in 10percent of patients. In low incidence areas rapidly enlarging liver without evidence of cirrhosis is the usual pattern.
- Pyrexia of undetermined origin, with localizing signs – tenderness in the epigastrium and right upper quadrant; leucocytosis is common and distinction from amoebic liver abscess is difficult, especially in the Tropics and may need to be carried out through a therapeutic trial with metronidazole.
- Cholestatic jaundice.
- Spontaneous haemoperitoneum from rupture of a hepatic nodule.
- Appearance of metastatic lesions pulmonary signs, ascites, umbilical and other skin nodules.
- Endocrine dysfunction – from humoral products released by the tumour: hypercalcaemia, hypoglycaemia and hyperthyroidism.

Surveillance for HCC

In low incidence countries and also to an increasing frequency in high incidence localities presentation is not so florid, raising the need for a high index of suspicion for early diagnosis through screening or

surveillance. Surveillance should be offered in the setting of a programme in which screening tests and recall procedures are standardized and in which quality control procedures are in place. It also involves decision on what level of risk of HCC is high enough to trigger surveillance, what tests to use and how frequently (surveillance interval).

In a landmark publication Bruix and Sherman have analysed and synthesized the guidelines issued by several key international liver study groups including the American College of Physicians, Manual for Assessing Health Practices and Designing Practice Guidelines, American Association for Study of Liver Disease (AASLD), and the European Association of Study of the liver (EASL) into the surveillance recommendations detailed in Table 3.

Table 3

HEPATITIS B CARRIERS	NON-HEPATITIS B CIRRHOISIS
Asian males ≥ 40 Asian females ≥ 50 All cirrhotic hepatitis B carriers Family history of HCC Africans over age 20 <i>For non-cirrhotic hepatitis B carriers not listed above, the risk of HCC varies according to severity of the underlying disease and current and past hepatic inflammatory activity. Patients with high HBV DNA concentrations and those with ongoing hepatic inflammatory activity remain at high risk of HCC</i>	Hepatitis C Alcoholic cirrhosis Genetic haemochromatosis Primary biliary cirrhosis <i>Although the following groups have an increased risk of HCC no recommendations for or against surveillance can be made because a lack of data precludes an assessment of whether surveillance would be beneficial.</i> Alpha-1 antitrypsin deficiency Non-alcoholic steatohepatitis Autoimmune hepatitis

Recommendation 1: Patients at high risk for developing HCC listed in Table 1 should be entered into a surveillance programme.

Recommendation 2: Patients on transplant waiting list should be screened for HCC because development of HCC should confer increased priority for liver transplantation and also because failure to screen for HCC means that patients may develop HCC and progress beyond listing criteria without the physician being aware.

Recommendation 3: Surveillance for HCC should be performed using ultrasonography; it has sensitivity between 65 to 80% and a specificity of 90%.

Recommendation 4: α-fetoprotein should not be used for screening unless ultrasound is not available but, α-fetoprotein alone should not be used because of its high sensitivity with associated high false positive rates

(>5%). However in Ghana where ultrasound facilities are not universally available a high level of fetoprotein (> 200ng/ml) may raise high level of suspicion

Recommendation 5: The ideal surveillance interval is not known but based on tumour doubling times this should be 6-12months.

Recommendation 6: If there is no a priori reason to suspect existence of HCC the surveillance interval need not be shortened for patients at higher risk of HCC.

Diagnostic Tests In HCC

Imaging (ultrasound, CT, MRI), α -fetoprotein, serology and tissue biopsy are the principal modalities for confirmation of HCC diagnosis. The context determines the order of preference, but imaging, particularly ultrasound is useful in determining the extent of the lesion. For an incidental lesion, detected by ultrasound the sequence of tests depends on the size of the lesion.

Lesion >2cm in Diameter

In a cirrhotic liver an ultrasound detected mass in excess of 2cm is highly suspicious of HCC. It is generally agreed that if the α -fetoprotein level is higher than 200ng/ml and the radiological appearance of the mass is suggestive of HCC (i.e. multifocal with arterial hypervascularity) the probability of HCC is so high that tissue biopsy may not be necessary, unless the imaging appearance is atypical²⁹. The EASL conference confirms this but recommends that femoral arterial vascularization is seen in two imaging modalities-CT and MRI.

Lesion 1-2cm in Diameter

The EASL conference is of the view that lesions of this order need to be biopsied irrespective of the vascular profile on imaging³⁰. Where biopsy turns up negative, the lesion needs to undergo enhanced follow up with CT/MRI.

Lesion less than 1cm in Diameter

A small lesion in a cirrhotic liver is less likely to be malignant particularly if it shows no contrast uptake on dynamic imaging. None-the-less such a lesion needs to be followed up at 3-6month intervals until the nodule either disappears, enlarges or displays diagnostic features of HCC.

Management Of HCC

Staging Systems

The principal challenge to management of HCC currently, is the lack of a validated staging system of assessing prognosis which aside from allocating the appropriate pathological status of the disease at presentation, also incorporates the functional status of such a complex organ as the liver and thus guides

choice of management modalities. Historically the TNM or Okuda systems predominated. Currently the Barcelona-Clinic Liver Cancer (BCLC, Fig. 1) staging system is the only one that takes account of the tumour stage, liver functional status, physical status and cancer related symptoms and thus links staging to treatment modalities and also with evidence based information on life expectancy³¹.

Historically diagnosis of HCC was nearly always made late with significant liver dysfunction, when practically all treatment modalities had little impact, but rather threatened additional morbidity from side effects. Regretfully this situation persists today in many developing countries. However a few are being seen with minimal symptoms and with well preserved liver function. Given the complexity of the disease and the large number of promising therapeutic measures, patients need to be referred to multidisciplinary teams (MDTS) consisting of Hepatologist, Pathologists, Radiologist, Surgeons and Oncologists. This is a daunting requirement for many sub Saharan African countries; membership of the MDTS may thus be adjusted to cover the currently available effective treatment modalities. The therapies known to offer a high rate of complete response or potential cure are surgical resection, transplantation and percutaneous ablation.

Surgical Resection

This is the therapeutic procedure of choice in non-cirrhotic patients who constitute only 5% of cases in Western countries, less in sub Saharan Africa but up to 40% in Asia, reflecting the epidemiological peculiarities of the disease. Careful selection procedures are needed for HCC patients with varying degrees of cirrhosis to diminish the risk of post operative liver failure; in general in these patients right hemi-hepatectomy carries a higher risk of liver decompensation than left hemi-hepatectomy.

The Child-Pugh classification has not proven reliable selection criteria as even Child-Pugh A patients have been shown to have significant liver function impairment. Many Japanese groups rely on the Indocyanine-Green retention test, but in Europe and North America the gold standard is constituted by normal bilirubin and absence of clinically significant portal hypertension measured by hepatic vein catheterization – a pressure of <10mmHg.

Most groups restrict the indication for resection to patients with single tumour in a suitable location for resection. The size of the tumour is not a clear-cut limiting factor although larger tumours, with increasing likelihood of vascular invasion carry a risk of increased incidence of recurrence. Chemo-embolisation of the tumour prior to resection offers no survival benefit³². Patients so selected achieve a 5-year survival rate of

over 70%. Recurrence rates could be as high 70% suggesting that these are the result of dissemination from the primary tumour rather than metachronous tumours developing in a cirrhotic liver. Where post-operative pathological studies reveal vascular lesions or satellites some workers have proposed immediate listing for transplantation. The limited resectional experience of the liver group in Accra, Ghana, yet to be published includes six cases over a period of three years, all late stage disease cases, involving three liver segments, with an average survival of 14 months (Disease Free State -DFS)

Liver Transplantation

Hepatocellular carcinoma patients were early candidates for liver transplantation because of the dismal life expectancy but experience from France, Italy and Germany have confirmed it as an effective option for patients corresponding to the Milan criteria: solitary tumour ≤ 5 cm or up to three nodules each < 3 cm³³. Living donor transplantation can be offered for HCC if the waiting time is long enough to allow tumour progression leading to exclusion from the waiting list. The 5-year survival of these early stage patients exceeds 70%. In Ghana there is, currently, no such facility for liver transplantation.

Percutaneous Ablation

This appears to be the best treatment for patients with early stage HCC who are not suitable for transplantation. In some Japanese centres this is offered as the first therapeutic option and may be a bridge to transplantation. There are as yet no Randomized Controlled Trials comparing local ablation to resection. A whole range of chemicals (ethanol, acetic acid, boiling saline) or physical agents (radiofrequency, microwave, laser and cryotherapy) have been applied but percutaneous ethanol injection under ultrasound guidance has been the best studied and most effective, achieving 90-100% necrosis in lesions < 2 cm, but reduces to 70% in 2-3cm lesions. Long term survival in Child Pugh A patients may be as much as 50% at 5 years.³⁴

The method seldom achieves complete necrosis in tumours larger than 3cm. Radiofrequency is more effective in larger tumours but due cognizance should be taken of side effects such as pleural effusion and peritoneal bleeding. The liver study group in Accra, Ghana has an ongoing local ablation programme using ethanol. A total of 6 patients with wide ranging demographics, but with hepatic solitary lesions > 5 cm have been treated, from time to time, with a series of ethanol injections (200ml per session). The survival period has ranged from 6 months to 18 months (Unpublished data). The small number of patients reflects the late and advanced presentations of most patients.

Palliative Treatment

Several palliative measures with marginal anti-tumour activity have shown no impact on survival in HCC. Chemotherapeutic agents, (usually adriamycin) delivered systemically inflict significant morbidity without survival benefit. Multiple treatment modalities – octreotide, interferon, tamoxifen, external radiation have been similarly ineffective. The only option for which there is positive information is transarterial chemoembolization. The latest most promising palliative chemotherapy has been the use, in 2007, of Sorafenib (Nexavar, Bayer) in advanced disease. This agent is a multikinase inhibitor given orally. Sorafenib achieved a survival (or progression free) period of between 6.5 -10.7 months as opposed to 4.2 - 7.9 in placebo groups^{34,36,37}. Given the dismal survival rate of the average Ghanaian patient this is a step forward. There are side effects such as the hand-foot syndrome, fatigue, but the major drawback is the cost (\$5,400, £2,980 per month) which is well beyond the pocket of most Ghanaian HCC patients.

Transarterial Chemoembolization

The intense neo-angiogenic activity of HCC makes it susceptible to arterial devascularizing agents, producing ischaemic tumour necrosis – the process of transarterial embolization (TAE). When this is combined with prior injection of chemotherapeutic agents, often mixed with lipiodol into the hepatic artery, transarterial chemoembolization (TACE), an extensive tumour necrosis is induced in more than 50% of patients. This can be ascertained in dynamic CT and MRI studies. Cumulative meta-analysis of published RCT indicates that patient survival is significantly improved.

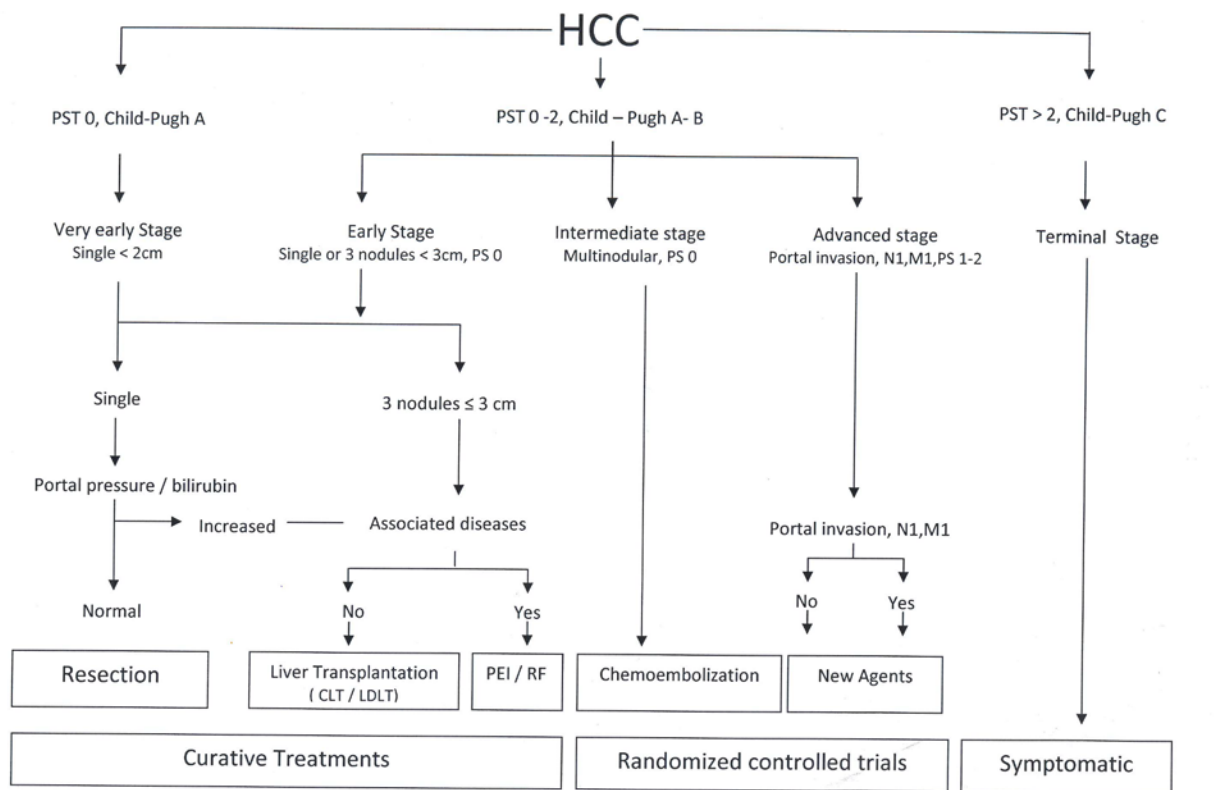
Conclusion

It is evident from this review of the molecular pathogenesis, detection, diagnosis and management of HCC that much remains to be done, not only on the identification of biomarkers to establish cancer risk and/or detect its appearance in a pre-clinical stage, but particularly in the high incidence areas of sub Saharan Africa, the need to identify effective adjuvant therapies for the teeming numbers of patients with advanced HCC.

This atmosphere of gloom can only be lifted by determined attempts to identify and treat the earlier asymptomatic cases occurring in the population alongside these advanced cases through functional surveillance programmes, targeting the at-risk population of HBV and HCV chronic infections, as well as voluntary screening for HBsAg and anti-HCV. In addition serological tests including viral load as well as cost for treatment should be subsidized (or included in the NHIS). It will take several years before the high prevalence of HBV and HCV infections decline; in the

meantime hepatocellular carcinoma in Ghana is likely to show upward trend, affecting the relatively young who are the family bread-winners and form the backbone of the economy. More research efforts need to be made in the documentation of the commonest malignancies in sub Saharan Africa through reactivation of the work of functional National Cancer the recent inclusion of HBV vaccination in the national

immunization programmes in several countries and Registries in the region. The time to act is now. Finally there is the need for active follow up on the impact of the recent inclusion of HBV vaccination in the national immunization programmes in several countries and especially Ghana. This is a function that can be assigned to the rejuvenated National Cancer Registries.



Strategy for staging and treatment assignment in patient diagnosed with HCC according to the BCLC proposal.

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