The Clinical and Pathological Features of Hepatocellular Carcinoma in Nnewi, Nigeria

1.okonkwo U. C., 1.**nwosu M. N., 2.Ukah C., 3.Okpala O. C., 2. Ahaneku J. I.**

1. Department of Medicine, 2. Department of Pathology, 3.Department of Radiology, Nnamdi Azikiwe University Teaching Hospital, P.M.B 5025, Nnewi, Anambra state, Nigeria.

Dr. Okonkwo UC, the principal author evaluated the patients and wrote the article.
Dr. Nwosu MN, contributed to the discussion.
Dr. Ukah C, reported the histopathological features of the liver biopsy specimens.
Dr. Okpala OC, performed and reported the abdominal ultrasound.
Prof. Ahaneku JI supervised the laboratory investigations.

ABSTRACT

BACKGROUND: Hepatocellular carcinoma (HCC) remains the commonest malignancy of the liver. In spite of the recent advances in treatment, prognosis is still abysmal especially in developing countries. This article aims to review the clinical and pathological features of HCC in a tertiary hospital at Nnewi.

METHOD: This was a cross-sectional study. Patients with HCC seen at the Medical Out-patient Department or admitted into the Medical wards of the Nnamdi Azikiwe University Teaching Hospital Nnewi were recruited. The study lasted from June 2007 to May, 2008. Subjects were clinically evaluated and blood samples collected for HBsAg, anti-HCV and HBeAg assays.

RESULTS: The prevalence of HCC was 2.4%. Of the 60 patients studied, 38 were males and 22 were females with a male to female ratio of 2:1. Their ages ranged from 19-86years with a mean age of 50.62±17.54. The mean duration of symptoms before presentation was 16weeks and the mean duration from onset of symptoms to death is 20weeks. Common presenting symptoms were painful right hypochondrial mass, abdominal swelling, weight loss, early satiety and fatigue while coagulopathy, ascites and hepatic encephalopathy were the most common complications. Multiple lesions affecting both lobes of the liver was seen in 48 patients on ultrasound, 36.6% were positive for HBsAg of which 41% were HBeAg positive. HCV antibodies were present in 8.3% of the patients. Well differentiated HCC of the pseudo-glandular variety was the most common histological type.

CONCLUSION: HCC affects middle aged Nigerians. Though well differentiated, it presents late with clinical features of advanced disease leading to death within six months. It is more often associated with chronic HBV than HCV infection.

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for 5.6% of all human cancers. It is the fifth most common cancer in men and eight most common in women worldwide and is the third leading cause of cancer related death, exceeded only by cancers of the lung and stomach.[1]. The World Health Organization (WHO) in the year 2003 reported that between five hundred thousand and one million new cases occur per year[2]. However, significant differences exist between and with-in countries. Most cases of HCC occur in Asia and sub-Saharan Africa. In Africa, the highest incidence was documented among the Bantu males in Mozambique[3]. In Nigeria, the prevalence of HCC increases as one migrates from the Southern rain-forest to the Northern savanna.[4,5,6]. A prevalence of 0.4% was recorded in Port Harcourt south-south of Nigeria. In Ibadan, South-western Nigeria and Maiduguri, North-east of Nigeria, incidence of 4.91and11.2 per 1000 patients per year has been documented respectively. This difference in prevalence closely mirrors the HBs Ag carrier status in these geographic regions.

The incidence of HCC is increasing both in the developed and developing countries[7]. This has been attributed to the rising prevalence of its risk factors; alcohol consumption, non-alcoholic fatty liver disease (NAFLD) associated with type 11 diabetes and obesity and especially chronic hepatitis B and C infection. Despite the advances in treatment, the prognosis of HCC is still poor. This is more so in a developing country like Nigeria where late presentation coupled with paucity of diagnostic and interventional facilities have rendered the tumor untreatable. This is in contrast to what obtains in the developed countries where diagnosis of the tumor in the early stages makes institution of intention-to-cure therapies possible with 5-year survival approaching 70-80%[8]. This study was carried out to assess the clinical and pathological features of HCC in patients presenting at the Nnamdi Azikiwe University Teaching Hospital, Nnewi, South-eastern Nigeria.

PATIENTS AND METHOD

This cross-sectional hospital based study on the clinical and pathological features of hepatocellular carcinoma was carried out among adult patients presenting consecutively at the Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi. The hospital is a 238 bed tertiary health center serving all the towns in Anambra state and part of neighboring states like Abia, Delta, Imo and Enugu states. The Medical Out-patient

Correspondence: Dr. U.C. Okonkwo, Nnamdi Azikiwe University Teaching Hospital, P.M.B. 5025 Nnewi, Anambra state, Nigeria.
Mobile: 08033251240, Email: ucsuizes@yahoo.co.uk.

Department and the Medical wards of this hospital were the areas of the study.

Sixty consecutive adult (18years and above) subjects with clinical features and ultrasound diagnosis of HCC were recruited from June 2007 to May 2008. Patients with evidence of a primary source of malignancy other than the liver were considered to have metastatic liver disease and were excluded from the study. A written informed consent was obtained from each person in the presence of a witness to collect blood specimen and undergo a liver biopsy. A structured questionnaire on personal data, present and past symptoms of HCC was administered to each subject. A detailed physical examination was performed and findings documented. Eight milliliters (mls) of venous blood was drawn from the ante-cubital fossa under strict aseptic conditions and with observance of universal precautionary measures. Two mls of blood was put into an anti-coagulated bottle for prothrombin time. Six mls was put in a plain bottle for HBsAg and anti-HCV assays using the heamaglutination method (Acumen diagnostics, India); HBeAg was assayed for those who were HBsAg positive using ELISA method (Clinotech Diagnostics, Canada). All the patients had abdominal ultrasonography using a 3.5-mega Hz linear real-time transducer of Dynamic Imaging limited Scotland, UK. Patients without coagulopathy, massive ascites and hepatic encephalopathy were offered liver biopsy and a blind percutaneous liver biopsy using Menghini needle was carried out on those who gave their informed consent. Liver biopsy specimens were processed and stained with haematoxylin and eosin (H&E), Masson trichrome and reticulin stains and characterized.

ETHICAL CLEARANCE

Ethical clearance was obtained from the Nnamdi Azikiwe University Teaching Hospital Ethical Committee the on 8th day of May, 2007.

RESULTS

Sixty consecutive patients out of a total of 2449 patients seen at the Medical Out-patient Department or admitted into the Medical wards were recruited for this study. The prevalence of HCC was 2.4%. There were 38 males and 22 females giving a male to female ratio of approximately 2:1. The ages ranged from 19-86years with a mean age of 50.62±17.54. The mean ages of males were 50.39±16.95 and that of females were 51± 18.34. There was no statistical difference between the mean ages of males and females with HCC (p=0.52). The age range 50-59years had the highest prevalence of the disease. (Table 1)

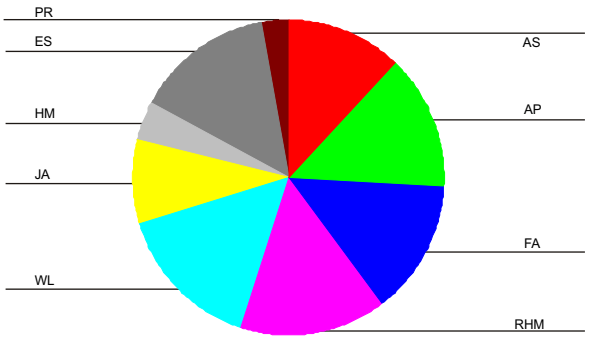
Table 1: AGE AND SEX DISTRIBUTION OF THE PATIENTS WITH HCC.

AGE (years)	SEX		TOTAL	PERCENT
	MALE (%)	FEMALE (%)		
<20	-	1 (1.7)	1	1.7
20-29	6 (10)	2 (3.3)	8	13.3
30-39	5 (8.3)	4 (6.7)	9	15
40-49	5 (8.3)	1 (1.7)	6	10
50-59	11 (18.3)	8 (13.3)	19	31.3
60-69	7 (11.7)	2 (3.3)	9	15
70 and above	4 (6.7)	4 (6.7)	8	13.3
TOTAL	38 (63.3)	22 (36,7)	60	100

Chi Sq. = 5.127, P = 0.52

Duration of symptoms before presentation ranged from 2-56weeks with a mean of 16weeks (SD±15.8). One-third of the patients presented within 2 months of the onset of their symptoms. The common presenting symptoms were; right hypochondrial mass (90%), abdominal pain (83%) abdominal swelling (72%), easy fatiguability (83%), early satiety (87%) and weight loss (92%). (Fig 1).

Fig 1: PATTERN OF CLINICAL PRESENTATION OF HCC



AS= Abdominal swelling, AP= Abdominal pain, WL= Weight loss, FA= Fatigue, JA= yellowness of the eyes
HM = Haematemesis/melaena, ES= Early satiety, RHM= right hypochondrial mass,
PR= pruritus.

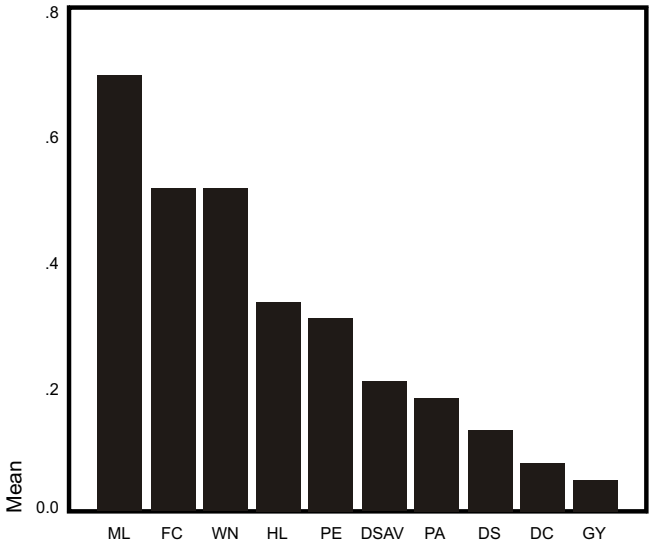
The major clinical findings on examination were hepatomegaly (90%), ascites (71.7%), encephalopathy (58.3%), Jaundice (38.3%), and splenomegaly (31.7%). Of the 54 patients with hepatomegaly, 14 (23.3%) had arterial bruit. The ascitic fluid was haemorrhagic in 12(28.3%) of the 42 patients with ascites. Twenty-nine (48.3%) patients had both ascites and leg oedema. Upper gastrointestinal bleeding manifesting as haematemesis and/ or melena stool was documented in only14 (23.3%) of the 60 patients with HCC. Coagulopathy (prothrombin time prolonged by more than 3 seconds) was seen in 47 (78.3%) patients, anaemia was present in 54.8% of the 55 patients who had haemoglobin result. Of these, 4 (13%) had severe anaemia, and all four presented with haematemesis. Table 2 shows the common complications of HCC.

Table 2: COMPLICATIONS OF HCC

COMPLICATION	NUMBER (%)
COAGULOPATHY	47 (78.3)
ASCITES	42 (70)
HEPATIC ENCEPHALOPATHY	35 (58.3)
UPPER GASTRO-INTESTINAL BLEEDING	14 (23.3)
INTRAPERITONEAL HAEMORRHAGE	12 (28)

The stigmata of chronic liver disease (CLD) detected on the patients were finger clubbing 31(51.7%), wasting of the small muscles of the hand 37(61.7%), leuconychia 29(48.3%), palmar erythema 20 (33%), loss of axillary/pubic hair 27 (45%), darkening of skin 9 (15%), parotid enlargement 7(11.7%), caput medusae 10(16.7%), Dupuytrens contracture 3(5%) and 2(5.6%) out of the 38 males had gynaecomastia.(Fig 2)

Figure 2: Stigmata of chronic liver disease in HCC patients.



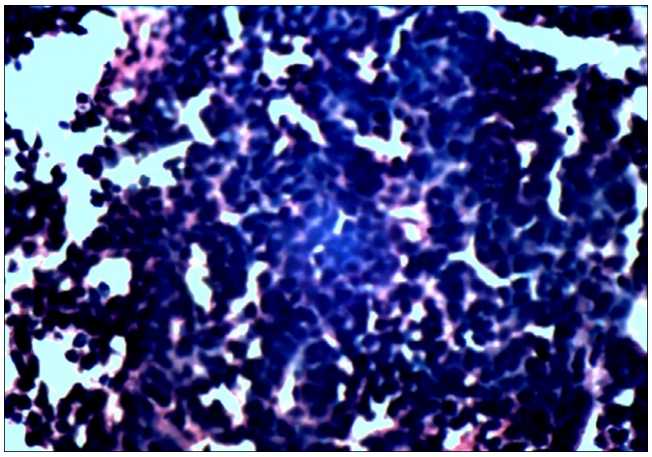
ML= muscle wasting, FC= finger clubbing, WN= leuconychia,
HL= loss of axillary/pubic hair, PE= palmar erythema,
DSAV= distended superficial abdominal veins, PA= parotid enlargement
DS= darkening of skin, DC= Dupuytren's contracture, GY= gynaecomastia

On ultrasound, the finding of coarse irregular internal echoes that were hypo/hyper-echoic with posterior acoustic shadows in all of the patients formed the basis of diagnosis of HCC. Forty-eight patients had multiple lesions in both lobes of the liver, 7 had lesions in only the right lobe while 5 had lesions affecting only the left lobe. Thirty-seven (62%) patients were reported as having underlying liver cirrhosis seen as coarse irregular hepatic parenchyma associated with multiple echogenic linear strands.

Eighteen patients were eligible for liver biopsy but only 10(16.7%) gave their informed consent and had histological confirmation of the diagnosis. Typical histological features were demonstrated in all but two of the patients who were reported to have inadequate specimen.

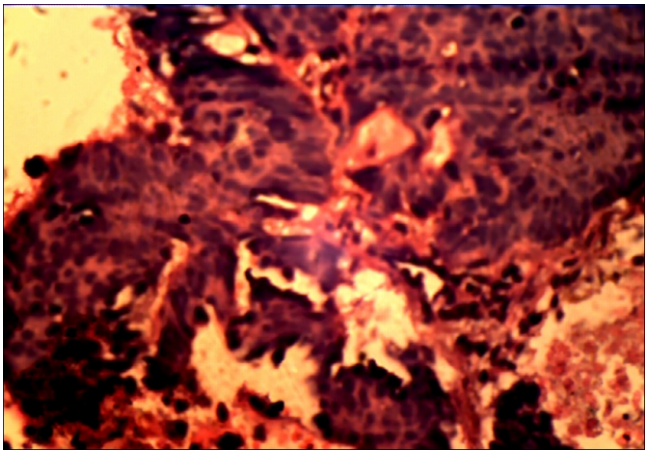
Macroscopically, specimen appeared grayish white and friable with the smallest measuring 0.2x0.2x0.1cm and the largest measuring 0.8x0.5x0.4cm. Microscopically, 5 (62.5%) of the specimens were well differentiated with nodular fragments of mildly pleomorphic polygonal hepatocytes that are between 3-4 cell layer thick arranged in irregular anastomosing pattern and separated by pseudo-acini. The cells had increased nucleo-cytoplasmic ratio with areas of necrosis. The pseudo-glandular pattern was found in all the well differentiated HCC. Three specimens (37.5%) were highly pleomorphic with grade 3 nuclei. They showed high mitotic rate with extensive areas of tumour necrosis and were reported to be undifferentiated. Of the eight specimen analyzed, 4(50%) were associated with liver cirrhosis and were all well differentiated. Figures 3 and 4 each depict the micrograph of a well-differentiated and an undifferentiated HCC respectively.

Figure 3: Micrograph showing a well differentiated HCC



The hepatocytes are arranged in more than two cell layers separated by pseudo acini. The nuclei are hyper chromatic with increased nucleo-cytoplasmic ratio

Figure 4: Micrograph showing anaplastic HCC



The hepatocytes are highly pleomorphic with hyperchromatic nuclei
The cells exhibit grade 3-4 nuclei with absent cytoplasm
An area of necrosis is clearly shown on the right lower margin.

HBsAg was positive in 22 out of the 60 patients studied. The prevalence of HBsAg was 36.6%. Out of the 22 patients who were positive for HBsAg, 18(82%) were males and 4 (18%) were females. HBeAg was positive in 9(40.9%) of the 22 patients whose sera tested positive to HBsAg. Five patients were anti-HCV positive giving it a prevalence rate of 8.3%. They were 4 males and one female. Co-infection of HBV and HCV was found in 3 patients. There was a significant correlation between Hepatitis B virus carrier status and gender (p= 0.024). This was not observed for HBeAg and anti-HCV(p >0.05) respectively (Table 3).

Table 3: Prevalence of HBsAg, HBeAg and Anti-HCV among Patients with HCC.

Viral Factor	MALE N= 38 (%)	FEMALE N= 22 (%)	TOTAL *N=60 (%)	Chi square	p-value
HBsAg +	18 (47.3)	4 (18.1)	22 (36.6)	5.111	0.024
HBsAg	20 (52.6)	18 (81.8)	38 (63.3)		
*HBeAg+	8(36.3)	1 (4.5)	9 (40.9)	0.512	0.474
*HBeAg-	10 (45.4)	3 (13.6)	13 (59)		
Anti-HCV+	4 (15)	1(3.3)	5 (8.3)	0.652	0.419
Anti-HCV-	34 (85)	21 (96.7)	55 (91.6)		

HBsAg = Hepatitis B surface antigen

HBeAg = Hepatitis B e antigen

Anti-HCV =Antibodies to Hepatitis virus

*Total = 22

Thirty-five patients died on admission. All received only palliative care. The rest were either discharged on request or against medical advice. The mean duration from onset of symptoms to death was 20weeks**.** The main causes of death were hepatic encephalopathy (51.4%), Upper gastro-intestinal bleeding (34.2%) and intra-peritoneal rupture of the tumour (14.2%).

DISCUSSION

Hepatocellular carcinoma is one of the most common malignancies in the world[9]. Its prevalence is determined by that of its risk factors particularly viral hepatitis B. Therefore, particularly high rates are found in sub-Saharan Africa where HBV is endemic[7]. In Nigeria, it is the commonest cause of cancer in the medical wards and the most common cause of cancer-related death in middle aged and elderly Nigerians[10].

Our study showed that HCC predominantly affects middle aged Nigerians. The mean age of the cases was 50.6±17.5 years. Nwosu *et al*[11] had earlier reported a mean age of 46±9.2 years among HCC patients in Nnewi. The mean ages of 48.6±14.7 and 43.17±14.7years had been reported from Maiduguri and Enugu respectively[12,13]. This reiterates the fact that in regions of high endemicity, HCC is a disease of the young and middle age group unlike what obtains in low endemic regions. This epidemiological difference has been related to the mode of transmission of HBV which is acquired in childhood through vertical and horizontal transmission in endemic populations but is acquired in adulthood through sexual and non-sexual close contact in non endemic regions.

The male to female ratio was 2:1 and there was a significant correlation between HBsAg status and gender. This is a confirmation of global and national trend that HCC is more common in males. Although not fully understood, the differences in sex distribution may be due to variations in hepatitis B virus carrier status as shown in this study, exposure to environmental toxins and trophic effects of androgens[7].

The pentad of painful right hypochondrial mass, abdominal swelling, weight loss, early satiety and fatigue were the common presenting symptoms. This is similar to what was obtained in previous studies though fatigue was not considered in those studies probably because of its lack of specificity[12,13]. Arterial bruit over an enlarged liver is considered a reliable diagnostic sign. However, this was elicited in only 23% of the patients indicating that it is not a common finding in HCC. Jaundice was present in only 38% of the patients and this is in keeping with reports that jaundice is not a usual feature of HCC occurring in less than fifty per cent of cases and is said to be usually mild[4]. Mild-moderate anaemia was present in 54% of the patients. None of the patients had haemoglobin values in the polycythemia range (highest recorded was 12g/dl) indicating that erythrocytosis is not a common feature of HCC among our patients. However, it may be possible that chronic malnutrition and hook worm infestation with the attendant chronic anaemia prevalent in our community may obscure the presence of this para-neoplastic manifestation.

Most of the patients presented late with at least one or more features of de-compensation; nodular hepatomegaly, hepatic encephalopathy, upper gastro-intestinal bleeding and ascites. The mean duration of symptoms before presentation was 16 weeks and for the 35 (58.3%) patients who died on admission, the mean duration from onset of symptoms to death was 20weeks.These findings are typical of HCC in sub-Saharan Africa including Nigeria where late presentation and rapid downhill course excludes the prospects of therapy with curative intervention leading to abysmal prognosis[14]. This contrasts with what is obtained in Europe and America where regular surveillance of high risk patients aid in early diagnosis and institution of therapy with curative intent[8].

By comparing the prevalence of HBsAg and anti-HCV among the HCC patients, there was a higher prevalence of HBsAg (36.7%) than HCV (8.3%). This shows that HCV is not as important as HBV in the aetiology of HCC in our environment and it is consistent with findings from other studies in Nigeria[12]. The prevalence of HBsAg among the HCC patients in this study compares with 37.6% reported in Port Harcourt but lower than and 67% reported in Maiduguri[4,12]. This may be explained by the increasing prevalence of hepatitis B virus as one migrates from the Southern delta towards the Northern savanna of Nigeria[4,12].

Of the 22 subjects positive for HBsAg, only 9 (40.9%) tested positive to HBeAg. This is in keeping with report from another study in South-Eastern Nigeria that HBeAg positivity is low in patients who are HBsAg positive[15]. One may infer from this result that most of the infections are due to a pre-core mutant of HBV which is unable to secrete the e-antigen.

More than 70% of the patients presented in advanced disease with features of de-compensation. This explains why needle biopsy of the liver could not be performed on them coupled with poor patient acceptance of this procedure. Although liver biopsy is considered the gold standard in the diagnosis of HCC, its invasive nature, complications, and chances of obtaining un-involved hepatic parenchyma if not ultrasound guided had prompted international bodies involved in the study of the liver to adopt less invasive methods of diagnosis[16, 17]. Ultrasound has been shown to have good sensitivity (78%) and specificity (93%) in the diagnosis of HCC and the finding of a typical vascular pattern with arterial enhancement and portal venous "washout" on ultrasonography is accepted as one of the non-invasive criteria for the diagnosis of HCC[16,17,18].

Macroscopically, all of the liver biopsy specimens, appeared grayish white and friable suggesting that they were malignant. Microscopically, well differentiated

HCC of the pseudoglandular (pseudo acinar) pattern was the most common histologic variant seen in 5(62.5%) of the patients. Un-differentiated (anaplastic) HCC was seen in 3 (37.5%) of the patients. This is in keeping with the assertion that despite the aggressive nature of HCC, most tumours are well differentiated[19]. Four tumours (50%) occurred on a background of liver cirrhosis and is lower than findings from other centers[19,20]. This may be due to the small size of the sample.

It is concluded from this study that HCC affects mostly middle-aged males in Nnewi, Nigeria and they form the major workforce of any nation. HCC, though well-differentiated has a very poor prognosis because of late presentation. We advocate routine screening of all patients for risk factors of HCC especially HBsAg and anti-HCV. All those at risk should be placed under medical surveillance to enable early detection of the tumour. Patients who are HBsAg negative should be vaccinated against Hepatitis B virus if they are also anti-HBS negative.

We admit that a limitation of this study was the inability to have a histological diagnoses in all our patients because of the presence of advanced disease with features of decompensation at the time of presentation. Therefore, close differentials such as cholangiocarcinoma, though rare, may have been missed.

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