

## Liver Cancer in Enugu, South East Nigeria

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**Abstract: Background:** The incidence of liver cancer varies with geographical location. The diagnosis can be difficult and often requires the use of serum markers, one or more imaging modalities and histologic confirmation. The disease is frequently diagnosed late in its course because of the absence of pathognomonic symptoms and the liver's large functional reserve. This study was designed to highlight the clinical and laboratory characteristics of patients with primary liver cancer. **Method:** In this retrospective study, case notes of patients seen over a seven year period in a tertiary health facility in Nigeria, which is a high incidence country, were retrieved and analyzed to determine selected epidemiologic variables related to liver cancer. **Result:** There were 424 patients (294 male and 130 females) in whom a diagnosis of primary liver cancer was made. Their ages ranged between 1 year and 80 years with a mean of  $43.7 \pm 16.52$  years. The commonest clinical features were abdominal pain, weight loss, abdominal swelling, hepatomegaly, jaundice and pedal edema. B surface antigen was present in 61.5% of patients while HCV antibody was present in 11.6%. Most of the patients who were admitted to hospital (62.9%) died. **Conclusion:** Late presentation is the main characteristic of liver cancer in Nigeria and the prognosis remains dismal. Hepatitis B virus infection is the main risk factor in majority of cases.

**Key words:** Liver cancer, hepatocellular carcinoma, epidemiology, hepatitis B virus

### INTRODUCTION

The liver is the largest organ in the body. Cancers affecting the liver may be primary or secondary (metastatic). Hepatocellular carcinoma (HCC) is the commonest primary cancer of the liver. It is 6th commonest malignancy worldwide and the 3rd leading cause of cancer-related death (Parkin *et al.*, 2005). Hepatocellular carcinoma has a heterogenous geographical distribution determined mainly by the presence of the risk factors in different parts of the world. It is more common in sub-Saharan Africa and South-East Asia than North America and Western Europe (Chuang *et al.*, 1992; Bosch *et al.*, 1999; Parkin *et al.*, 1999). Hepatitis B virus is the major hepatocarcinogen in Asia and Africa, where the infection is acquired early in life and thus becomes persistent in up to 75% of individuals (Colombo, 2003). In the Western world, Hepatitis C virus (HCV) is the leading cause of HCC, which develops in older, cirrhotic patients (Bruix *et al.*, 1989). Globally, about 80% of cases of HCC are due to underlying chronic hepatitis B and C infection (Perz *et al.*, 2006).

A distinct feature of HCC is the fact that prognosis is not determined only by the tumoral disease but also by the severity of the underlying liver disease. Many

patients who are diagnosed with HCC have advanced disease and are only candidates for palliative care, contributing to a relatively low reported 5-year survival rates of approximately 10% (London and McGlynn, 2006). In high prevalence areas many patients die within 6 months of diagnosis (Ndububa *et al.*, 2001).

There are several reports in Nigeria on epidemiology of liver cancer (Francis and Smith, 1972; Fakunle *et al.*, 1977; Ndububa *et al.*, 2001; Mandong *et al.*, 2003; Mustapha and Pindiga, 2003; Mustapha *et al.*, 2007). However, there is a relative dearth of published work on liver cancer from the South-Eastern part of Nigeria. This study was carried out with the objective of highlighting some of the etiological factors, clinical manifestations, laboratory findings and prognosis of liver cancer at the University of Nigeria Teaching Hospital Ituku/Ozalla, Enugu during a seven year period.

### MATERIALS AND METHODS

This was a retrospective study of patients managed for primary liver cancer at the University of Nigeria Teaching Hospital (UNTH) Ituku/Ozalla, Enugu, Enugu state, Nigeria. This hospital has a catchment area of mainly the South-Eastern states of Nigeria (Enugu, Ebonyi, Anambra, Imo and Abia). Patients from other

neighboring states like Rivers, Cross River, Akwa Ibom, Delta, Benue and Kogi also attend this hospital. These states have a population of about 40 million.

Case notes of patients diagnosed with primary liver cancer from January 1999 to December 2005 were retrieved from the medical records department of the hospital. Patients with a diagnosis of metastatic liver disease (with known primary site) were not included. Information extracted from the case notes included age, gender, presenting symptoms, risk factors for liver cancer, physical signs and results of relevant laboratory tests. The patients who were admitted to hospital in the course of management were further evaluated to determine the outcome of treatment.

The results were analyzed using the computer software SPSS version 12 and expressed as percentages, means and standard deviation. Difference between means was determined using student t-test and a  $p < 0.05$  was considered statistically significant.

**RESULTS**

There were 424 patients (294 males and 130 female) in whom a diagnosis of primary liver cancer was made during the seven year period. This constituted 9.7% of all cancers diagnosed during the period. Their ages ranged from 1 year to 82 years (Mean =  $43.73 \pm 16.43$  years) Table 1 illustrates the age and gender distribution of the patients. The mean age of the male patients was  $43.35 \pm 15.90$  years while the mean age of the female patients was  $44.26 \pm 17.23$  years. The difference between the two means was not statistically significant ( $p = 0.7031$ ).

The risk factors for HCC are described in Table 2. There was a positive history of alcohol consumption in 59.8% of the patients, 31.4% received injections from medical quacks, 14.7% received blood transfusion and 10.8% had multiple sexual partners. Intravenous drug use was practiced by only 2.4%.

The presenting symptoms were abdominal pain (88%), abdominal swelling (68.2%), easy satiety (66.9%), pedal edema (45.7%), abdominal mass (39.5%), haematemesis (17.6%) and pruritus (15.0%). The physical signs included hepatomegaly (74.0%), jaundice (63.0%), splenomegaly (37.5%) and distended abdominal wall veins (36.1%). Hepatic encephalopathy in varying degrees of severity was demonstrable in 5% of cases.

Hepatitis B surface antigen (HBsAg) was present in 61.5%, hepatitis C virus antibody (11.6%), raised serum alkaline phosphatase (61.5%), hyperbilirubinaemia (61.9%), prolonged prothrombin time (56.0%), hypoalbuminaemia (45.0%), raised serum alpha fetoprotein

Table 1: Age and gender distribution of patients with hepatocellular carcinoma

Age (Years)	No. of patients		Total
	Male	Female	
0-9	-	1	1
10-19	13	8	21
20-29	64	24	88
30-39	67	21	88
40-49	49	26	75
50-59	48	20	68
60-69	30	19	49
70-79	20	7	27
80-89	3	4	7
Total	294	130	424

Mean =  $43.17 \pm 16.52$  years

Table 2: Risk Factors for hepatocellular carcinoma

Risk factor	No. of patients	Percentage
Use of alcohol (n = 373)	223	59.8
Receiving injection from medical quacks (n = 248)	78	31.4
Scarification marks (n = 198)	52	26.3
Blood transfusion (n = 366)	53	14.7
Multiple sexual partners (n = 157)	53	10.8
Intravenous drug use (n = 124)	3	2.4

Table 3: Features of hepatocellular carcinoma

Clinical feature	No. of patients	Percentage
Abdominal pain (n = 383)	377	88.0
Weight loss (n = 380)	262	68.9
Abdominal swelling (n = 380)	210	68.2
Easy satiety (n = 329)	220	66.9
Abdominal mass (n = 380)	150	39.5
Haematemesis (n = 318)	56	17.6
Pruritus (n = 327)	49	15.0
Hepatomegaly (n = 404)	299	74.0
Jaundice (n = 413)	260	63.0
Pedal Edema (n = 396)	181	45.7
Splenomegaly (n = 392)	147	37.5
Distended abdominal veins (n = 252)	91	36.1
Ascites (n = 398)	143	35.9
<b>Laboratory finding</b>		
Hyperbilirubinaemia (n = 286)	177	61.9
Raised Alkaline phosphatase (n = 286)	176	61.5
Hyperbilirubinaemia (n = 286)	177	61.9
Raised Alkaline phosphatase (n = 286)	176	61.5
HBsAg Positivity (n = 270)	166	61.5
Prolonged Prothrombin time (>3 seconds prolonged above control) (n = 250)	140	56.0
Hypoalbuminaemia (n = 269)	121	45.0
Raised alpha feto protein (n = 150)	67	44.7
Anaemia (n = 341)	136	39.9
Thrombocytopenia (n = 329)	92	28.0
HCV antibody positivity (n = 198)	23	11.6
Thrombocytosis (n = 329)	21	6.4
<b>Ultrasonographic feature (n = 386)</b>		
Multiple discrete lesions	160	41.4
Diffuse lesion	130	33.7
Solitary lesion	96	24.9

(44.7%), anaemia (39.9%), thrombocytopenia (28.0%) and thrombocytosis (6.4%). Abdominal ultrasonography showed multiple discrete lesions in 41.4%, diffuse lesion in 33.7 % and solitary lesion in 24.9%. Table 3 illustrates the clinical features, laboratory findings and ultrasonographic appearances. The diagnosis of liver

**Table 4: Method of diagnosis of hepatocellular carcinoma**

Method of diagnosis	No. of patients	Percentage
Clinical features alone	40	9.4
Clinical features plus ultrasonography	265	62.5
Clinical features, ultrasonography and CT scan	33	7.8
Clinical features, ultrasonography plus histology	86	20.3
Total	424	100.0

**Table 5: Outcome in 264 HCC patients admitted to hospital**

Outcome	No. of patients	Percentage
Died	166	62.9
Discharged	87	33.0
Discharged against medical advice	8	3.0
Referred to other centers	2	0.7
Absconded	1	0.4
Total	264	100.0

cancer was made on the basis of clinical features alone in 9.4% of cases; clinical features plus ultrasonography (62.5%); clinical features, ultrasonography plus CT scan (7.8%); clinical features ultrasonography plus histology in 20.3% of cases (Table 4).

Two hundred and sixty four out of the 424 patients with liver cancer (62.3%) were admitted to hospital in the course of management (Table 5). Out of this number, 166 (62.9%) died, 87 (33.0%) were discharged, 8 (3.0%) left hospital against medical advice, 2 (0.7%) were referred to other centers and 1 (0.4%) absconded.

## DISCUSSION

Liver cancer remains an important cause of cancer morbidity and mortality in Nigeria (Francis and Smith, 1972; Fakunle *et al.*, 1977; Ndububa *et al.*, 2001; Mandong *et al.*, 2003; Mustapha and Pindiga 2003; Mustapha *et al.*, 2007). The mean age of patients with liver cancer in this study was 43.17±16.52 years with a peak in the age group 20-59 years. This is similar to the findings in Port Harcourt Southern Nigeria, Maiduguri, Northern Nigeria (Mustapha *et al.*, 2007) where the mean ages of patients with HCC were 42 years and 48 years respectively. In Ile Ife, South Western Nigeria, the peak age group is 40-59 years (Ndububa *et al.*, 2001). In North America and Western Europe the incidence of HCC tends to increase with age, reaching its highest prevalence among those aged 65 years (El-Serag, 2007; Parikh and Hymann, 2007), being rare before the age of 50 years (Bosch *et al.*, 2004). The male:female ratio in this study was 2.3:1. There is a male preponderance in HCC all over the world (Parkin *et al.*, 2005). This study and several others carried out around the country showed similar trend (Francis and Smith, 1972; Fakunle *et al.*, 1977; Ndububa *et al.*, 2001; Mandong *et al.*, 2003; Mustapha and Pindiga, 2003; Mustapha *et al.*, 2007).

In this study, the main risk factors for liver cancer were HBV infection and alcohol. High risk behaviors for

HBV infection were injection from medical quacks (31.4%) and scarification marks (26.3%). History of blood transfusion was obtained from 14.7% of the patients. Injection from medical quacks and scarification marks may be more important than blood transfusion in the spread of HBV infection. Hepatitis B carrier state is established predominantly in early childhood and majority of black African children acquire the infection as a result of horizontal transmission (Botha *et al.*, 1984; Kew *et al.*, 1997; Bosch *et al.*, 1999). Many studies have shown that Hepatitis B carriers are 100 times more likely to develop HCC than uninfected persons, with an annual incidence of 0.5% in non- cirrhotic cases and 2-6% in cirrhotic patients (Beasley *et al.*, 1981; Fattovich *et al.*, 1995).

The exact role of alcohol in the etiology of liver cancer in this study is difficult to ascertain because there was no information on the quantity consumed and the duration of consumption. However it is possible that alcohol may have played a role in some of the patients particularly in concert with HBV infection (Donato *et al.*, 1997; Ikeda *et al.*, 1998; Chen *et al.*, 2006).

The most frequent clinical features were abdominal pain (88.0%), abdominal swelling (68.9%), weight loss (68.2%) and easy satiety (66.9%). Similar presentations were reported in other studies (Ndububa *et al.*, 2001) and these generally reflect the problem of late presentation which is common in Nigerian patients. The presence of jaundice, pedal edema, distended abdominal wall veins, ascites, haematemesis and varying degrees of hepatic encephalopathy lends credence to the fact that most patients present at a time when the disease is advanced, with profound hepatocellular failure, portal hypertension and prospects of only palliative treatment.

In this study HBsAg was the only marker of HBV infection tested and it was positive in 61.5%. This would have been higher if other markers had been included. However this prevalence is comparable to what was found in other studies on HCC across the country (Francis and Smith 1972; Fakunle *et al.*, 1977; Ndububa *et al.*, 2001; Mandong *et al.*, 2003; Mustapha and Pindiga 2003; Mustapha *et al.*, 2007).

Hepatitis C Virus (HCV) antibody was positive in 11.6% of patients and this is consistent with the general view that HCV contributes less than HBV to the high incidence of HCC in Sub-Saharan Africa and South East Asia (Leung *et al.*, 1992; Di Bisceglie, 1997; Kew *et al.*, 1997). A prospective study in Maiduguri, Northern Nigeria gave an HCV antibody seroprevalence of 17.6% (Mustapha *et al.*, 2007), while other researchers working in Ibadan recorded a seroprevalence of 18.7% (Olubuyide *et al.*, 1997). Lesi in Lagos reported a prevalence of 12.2% (Lesi *et al.*, 2002) in patient with chronic liver disease.

Late presentation was common to virtually all the liver cancer patients in this study. Biochemical and haematological indices of advanced liver disease which were common in the patients were hyperbilirubinaemia; prolonged prothrombin time, hypoalbuminaemia, anaemia, thrombocytopaenia and thrombocytosis.

Diagnosis of liver cancer was made with ultrasonography in majority of the patients (62.5%). Histological confirmation was made in only 86 patients (20%). One patient out of the 86 had hepatoblastoma and this was a child of 1 year. The reasons for this low rate of tissue diagnosis include very late presentation and refusal of patients to have biopsy and post mortem examination. There is also the problem of diagnostic nihilism on the part of attending physicians. However there are reasons to believe that majority of the patients in this study had HCC. First the age and sex distribution of the patients are similar to what was obtained in studies on HCC in Nigeria (Francis and Smith, 1972; Fakunle *et al.*, 1977; Ndububa *et al.*, 2001; Mandong *et al.*, 2003; Mustapha and Pindiga, 2003; Mustapha *et al.*, 2007). The second point is that the association between HCC and HBV infection was amply demonstrated in this study (61.5% of patients had HBsAg). This association does not exist for other types of liver cancer. Furthermore, non of the patients had any other obvious tumor outside the liver. However in a minority of cases of metastatic liver disease the primary tumor may be difficult to demonstrate.

The ultrasonographic appearances of the cancers were basically 3: multiple discrete lesions (41.4%), diffuse lesion (33.7%) and solitary lesion (24.9%). Multinodular HCC is known to be more prevalent among patients with multiple risk factors for the cancer (Fasani *et al.*, 1999). This suggests that the risk factors for most of our patients with liver cancer may be multiple. Ultrasonography has a reasonable sensitivity and specificity in the diagnosis of HCC (Miller *et al.*, 1991). For majority of our HCC patients who present late when liver masses are already present on clinical examination, ultrasound is cost effective, quick and relatively accurate. False negative results with ultrasonography are more likely to be encountered in early lesions, which is certainly not the case in most of our patients.

The outcome in 264 HCC patients who were managed as in-patients showed that over 60% died in hospital. This is not surprising because the prognosis all over the world is generally dismal (Ndububa *et al.*, 2001; London and McGlynn, 2006).

In conclusion liver cancer is a major cause of cancer morbidity and mortality in Enugu, South Eastern Nigeria. Virtually all patients present very late when only palliative treatment is possible. Chronic infection with HBV remains the major etiological factor in most of the patients

suggesting that majority of the cancers are HCC. Receiving injection from medical quacks and scarification marks may be the dominant modes of HBV transmission in these patients. Alcohol may also play a significant role in the causation of this disease but its exact importance will be better defined in prospective studies. The outlook for majority of the liver cancer patients remains poor due to late presentation. The only hope for control is through prevention and immunization is the major weapon in that respect.

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