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A Comprehensive Overview of In-patients Treated for Hepatocellular Carcinoma at a Tertiary Care Facility in Tanzania

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Abstract

Hepatocellular carcinoma (HCC) is one of the commonest causes of cancer-related morbidity and mortality worldwide. However, only a limited number of studies on HCC have been conducted in Tanzania. We therefore conducted a cross-sectional study among in-patients treated for HCC in a tertiary referral hospital located in Dar es Salaam, Tanzania, in order to provide a concise description of the clinical characteristics and treatment options offered in the study setting. We identified 36 in-patients treated for HCC over a 6-month data collection period. Seventy-seven percent (n = 28) of the participants were males and about two-thirds (61.2%) were aged between 40 and 60 years. Majority (44.4% [n = 16]) of the patients had Child-Pugh class B and an Eastern Cooperative Oncology Group (ECOG) performance status of 2 (33.3% [n = 12]). Patients with tumors >6.5 cm and multinodular tumors (>3 nodules) accounted for 69.4% (n = 25) and 55.6% (n = 20), respectively. Portal vascular invasion and extrahepatic metastasis were respectively present in 27.8% (n = 10) and 25% (n = 9) of the patients. Of the study participants, only two had early-stage disease as per the Barcelona Clinic Liver Cancer (BCLC) staging system, corresponding to the observed tumor resection rate of 5.6%. The most frequently reported inoperable factor among the study participants was an ECOG performance status > 0 (n = 30 [83.3%]). Findings thus reveal a high proportion of late-stage diseases among participants that could have resulted in the observed low tumor resection rate. Initiatives to facilitate identification of the disease at an early stage are therefore paramount in optimizing care.

Keywords: epidemiology; hepatocellular carcinoma; liver cancer; liver resection; liver transplantation; Tanzania

Introduction

As of the year 2020, primary liver cancer was the seventh most frequently reported cancer and the second most common cause of cancer-related mortality worldwide (1). The highest incidence rates of primary liver cancer in the world have been reported in Asia and Africa (2). Hepatocellular carcinoma (HCC) is the commonest reported histological type globally (3). Approximately 46,000 new cases of HCC are reported in Sub-Saharan Africa each year. However, limitations in reaching a definitive diagnosis and poor

documentation in cancer registries might account for an underestimated disease burden (4).

The only potentially curative treatment options for HCC include tumor resection and liver transplantation (5). However, the majority of patients in Tanzania do not receive curative treatment owing to the presence of advanced disease on the index presentation to the health facilities. The lack of awareness of the disease, poor accessibility to healthcare facilities, and lack of screening programs are among the postulated reasons for late presentation (6).

The availability of tertiary surgical services for patients with surgical hepatobiliary conditions in Tanzania warrants the formulation of strategies that will aid detection of the disease at early stages in order to optimally utilize the available curative options. To our knowledge, a limited number of studies on HCC have been conducted in Tanzania, mainly focusing on describing the epidemiology of the disease (6, 7). Nonetheless, a concise description of patients with HCC presenting for care is required to aid the formulation of tailored strategies aiming at optimizing patient care. With such apprehension, we performed a study among in-patients diagnosed to have HCC at Muhimbili National Hospital, Tanzania, assessing the clinical characteristics and the treatments offered.

Materials and Methods

Study design, period, and settings

A cross-sectional descriptive study was conducted from September 2020 to February 2021 at Muhimbili National Hospital; a Tertiary referral hospital located in Dar es Salaam, Tanzania. The facility is equipped with a surgical and medical gastroenterology/hepatology unit, a pathology unit, an oncology unit, and an interventional/diagnostic radiology unit capable of providing tertiary-level healthcare services to patients suffering from HCC.

Participants selection

The study included patients diagnosed to have HCC by either of the following criteria: (i) a histological diagnosis; (ii) a definite radiological diagnosis consistent with Liver Imaging Reporting and Data System (LI-RADS) – 5; or (iii) the presence of a radiologically confirmed liver lesion with concurrent significantly elevated blood alpha-fetoprotein (AFP) levels (>400 ng/mL). Patients with any condition that precluded data collection (i.e., encephalopathy) were excluded from the study.

A purposive sampling technique was used in selecting the study participants. Over the 6 months of data collection, 36 in-patients identified through ward registries qualified for enrollment as per the inclusion and exclusion criteria.

Data collection and analysis

Data were collected using an interviewer-administered structured checklist. Sociodemographic information and symptomatology were gathered via face-to-face interviews, whereas clinical information was extracted from the medical records.

Information that was collected included the sociodemographic and clinical characteristics, that is, age, sex, the quantity of alcohol consumption, body mass index (BMI), hepatitis B infection status, Eastern Cooperative Oncology Group (ECOG) performance status, Child-Pugh class, evidence of liver cirrhosis (histological, radiological, or gross), and evidence of clinically significant portal hypertension (platelet count $<100 \times 10^9$/L, splenomegaly, and esophageal varices). Tumor-related characteristics that were collected included tumor size, number of tumors, involved lobe, evidence of portal invasion, AFP levels, evidence of metastasis, and the Barcelona Clinic Liver Cancer (BCLC) stage. Information on the treatments offered (i.e. surgical vs. nonsurgical) was also collected. Data were analyzed using IBM SPSS Statistics Version 23 and presented as frequencies, proportions, and ranges.

Ethical considerations

Ethical clearance for conducting this study was sought from the Muhimbili University of Health and Allied Sciences' Institutional Review Board (Ref. No.: DA.282/298/01.C/). Permission to collect data was granted by the Muhimbili National Hospital's Training, Research and Consultancy Unit. The study was performed in accordance with the ethical standards laid by the 1964 Helsinki declaration and its later amendments on comparable ethical standards.

Results

Sociodemographic and clinical characteristics

A total of 36 patients were enrolled in the study. Table 1 shows that 77.8% (n = 28) of the participants were males and about two-thirds (61.2%) were aged between 40 and 60 years. Excessive alcohol consumption (>60 g/day) was reported in 9 (25.0%) participants. Twenty (55.6%) participants had a normal BMI, whereas 13 (36.1%) were overweight. Viral Hepatitis B infection was confirmed in 22 (61.1%) participants. Only 6 (16.7%) participants were asymptomatic (ECOG-0), whereas 2 (5.6%) participants were bedbound (ECOG-4). The majority had a physical performance status of ECOG-2. Liver cirrhosis was evident in 15 (41.6%) participants; however, only 4 (11.1%) participants had clinically evident portal hypertension. Of the 36 participants, only 9 (25.0%) participants had a good operative risk (Child-Pugh class A).

Table 1: Sociodemographics and clinical characteristics.

Variables	Frequency (%)
Sex	
Male	28 (77.8)
Female	8 (22.2)
Age (years)	
<40	5 (13.9)
40–60	22 (61.2)
>60	9 (25.0)
Alcohol consumption	
Excessive consumption (>60 g/day)	9 (25.0)
Body mass index	
Underweight	2 (5.6)
Normal	20 (55.6)
Overweight	13 (36.1)
Obese	1 (2.8)
Hepatitis B status	
Positive	22 (61.1)
Negative	14 (38.9)
ECOG performance status	
Asymptomatic (0)[a]	6 (16.7)
Symptomatic but completely ambulatory (1)	7 (19.4)
Symptomatic, <50% in bed during the day (2)	12 (33.3)
Symptomatic, >50% in bed but not bedbound (3)	9 (25.0)
Bedbound (4)	2 (5.6)
Liver cirrhosis	
Yes	15 (41.6)
Clinically significant portal hypertension	
Yes	4 (11.1)
Child-Pugh class	
Good operative risk (A)	9 (25.0)
Moderate operative risk (B)	16 (44.4)
Poor operative risk (C)	7 (19.4)
Unclassified	4 (11.1)

ECOG, Eastern Cooperative Oncology Group.
[a]Fully active, able to carry on all pre-disease performance without restriction.

Tumor-related characteristics

As shown in Table 2, half of the participants had tumors sized between 6 and 10 cm, with the rest of the majority (38.2%) having tumors >10 cm. Multiple tumors were reported in 20 (55.6%) participants. Bilateral involvement of the liver lobes was observed in 15 participants (41.7%). Moreover, the right lobe was the most frequently affected (38.9%) among participants with unilobar involvement.

Table 2: Tumor-related characteristics.

Variable	Frequency (%)
Tumor size	
≤6 cm	4 (11.8)
6–10 cm	17 (50.0)
>10 cm	13 (38.2)
Tumor number	
≤3	16 (44.4)
>3	20 (55.6)
Involved lobe	
Right	14 (38.9)
Left	7 (19.4)
Both	15 (41.7)
Portal vein invasion	
Yes	10 (27.8)
Extrahepatic metastases	
Yes	9 (25.0)
Alpha-fetoprotein level (ng/mL)	
0–19	8 (22.2)
20–399	3 (8.3)
≥400	25 (69.4)
BCLC stage	
Early (A)	2 (5.6)
Intermediate (B)	1 (2.8)
Advanced (C)	16 (44.4)
Terminal stage (D)	14 (38.9)
Unstaged	3 (8.3)

BCLC, Barcelona Clinic Liver Cancer.

Portal invasion and extrahepatic metastasis was reported in 10 (27.8%) and 9 (25.0%) participants, respectively. The AFP levels were significantly elevated (>400 ng/mL) in 25 participants (69.4%). Of the 36 participants, only 2 (5.6%) had the early disease as per the BCLC staging system.

Operability

The most frequently reported inoperable factors among the study participants (Table 3.) included an ECOG performance status > 0 (n = 30 [83.3%]), tumor size >6.5 cm (n = 25 [69.4%]), and multinodularity (>3 tumors) (n = 20 [55.6%]). Of the 36 study participants, only 2 underwent tumor resection for curative intent, resulting in a resection rate of 5.6%.

Discussion

This study provides a concise clinical description of in-patients treated for HCC at Muhimbili National Hospital, highlighting the sociodemographic and clinical characteristics, tumor-related characteristics, and the tumor resection rate.

HHC has a male predilection at a male-to-female ratio between 1.3:1 and 5.5:1 (8, 9). A similar distribution of 3.5:1 male-to-female ratio was observed in this study. The reason for this gender disparity is not well understood (10); however, a complex hormonal interplay mediated by adiponectin, a hormone secreted by adipocytes, is responsible for the increased HCC risk in males. It has been shown that high levels of testosterone in males lower the circulating adiponectin levels via Jun N-terminal kinase (JNK) 1-mediated inhibition in the adipocytes. The low circulating adiponectin levels thus increase the proliferation of cancer cells due to the lack of activation of adenosine monophosphate–activated protein kinase (AMPK) and tumor suppressor p38-alpha at the hepatocyte level (11).

The age distribution of the disease in our study has more or less been similar to those described in other studies (12, 13), with majority of the participants presenting between the age of 40 and 60 years. Different epidemiological factors that could explain this occurrence include a rising incidence of noninfectious cirrhotic liver disease that commonly presents in the elderly, the widespread use of vaccination and antiviral therapies that provide long-term control of chronic Hepatitis B or C viral infections but delays the occurrence of liver cirrhosis and subsequent HCC, and the fact that hepatitis C virus contraction commonly occurs later in life, thus presenting with more severe consequences including an increased risk of developing HCC (14). Conversely, the small proportion of patients presenting with early onset HCC could be explained by a family history of Hepatitis B viral infection predisposing patients to early onset liver cirrhosis, which on its own is an independent risk of developing HCC (15).

The most potent risk factor for the development of HCC is liver cirrhosis (16), and this was observed in over two-thirds of the participants. However, cirrhosis is usually present in about 80–90% of patients diagnosed to have HCC (17). The low proportion of cirrhosis from the usual that was observed in the participants might be explained by low sensitivity in detecting liver cirrhosis for the commonest radiological imaging modalities used in the study settings (ultrasonography without elastography and computerized tomography scan) (18). The majority also had major risks for developing cirrhosis; these included excessive alcohol consumption (25%) and viral Hepatitis B infection (61%). Also, overweight and obesity as risk factors for developing liver cirrhosis (19) were observed in about a third of the participants. The high proportion of overweight could have been due to the use of unadjusted weight-for-ascites, which is a common encounter in cirrhotic patients.

Despite liver cirrhosis being reported in about a third of the participants, only 11% had clinically significant portal hypertension. However, the impact of portal hypertension on the surgical management of HCC is clinically crucial, with widespread guidelines considering portal hypertension as a contraindication for surgical resection (20). Moreover, evidence shows increased postoperative morbidity among patients with portal hypertension undergoing liver resection (21). Nonetheless, a favorable outcome can be achieved in a limited number of carefully selected patients (20, 22), commending the need to further stratify this group of patients.

The majority of the participants had a poor ECOG performance status and moderate–poor operative risk as per the Child-Pugh classification, thus obviating surgical resection as a treatment option. Guidelines such as the BCLC advocates non-surgical treatment for symptomatic patients

Table 3: Inoperable factors.

Factors	Frequency (%)
Tumor size >6.5 cm[a]	25 (69.4)
Multinodular tumors (>3)[a,b]	20 (55.6)
ECOG performance status >0[b]	30 (83.3)
Child-Pugh class C[b]	7 (21.9)
Clinically significant portal hypertension	4 (11.1)
Extrahepatic metastases[a,b]	9 (25.0)
Major vascular invasion[a,b]	10 (27.8)

ECOG, Eastern Cooperative Oncology Group.
[a]Adopted from the University of California, San Francisco expanded criteria for liver transplantation.
[b]Adopted from Barcelona Clinic Liver Cancer staging.

(i.e., ECOG > 0). However, majority of patients presenting in the study setting had an ECOG performance status of > 0, perhaps due to late presentation, concurrent occurring comorbidities, or a fulminant course of the disease. With such an apprehension, further studies are needed to assess the safety of surgical management in this group of symptomatic patients and further sub-stratify patients that might benefit from curative surgical treatment since an ECOG of > 0 was the most frequently reported inoperable factor.

Tumor size and multifocality are some of the factors to be considered before deciding the modality of treatment, and most guidelines consider large tumor size and multifocality as contraindications for tumor resection (23, 24), both of which were among the frequently reported inoperable factors in our study. High levels of AFP have not been widely considered as a contraindication for resection; however, a positive correlation with tumor size has also been observed (25). Moreover, the levels of AFP can be used as a prognostic metric to guide treatment, where high levels are associated with poor prognosis and low levels with better prognosis (25, 26).

Bilobar involvement was observed in approximately 42% of the participants; nonetheless, bilobar disease should not be considered an absolute contraindication for curative surgical resection since surgery has been observed to result in a better survival outcome than non-resection therapies in this cohort of patients (27). Notwithstanding, major vascular involvement and extrahepatic metastasis were reported in over a quarter of the participants. Evidence shows that surgical resection does not confer a survival advantage in this group of patients, leaving nonsurgical approaches as the preferred alternative (25).

The core management of the HCC will mostly be guided by the overall stage of the disease. According to the BCLC guideline, surgical management (i.e., resection or liver transplantation) is only considered for stage 0 and stage A in the absence of commodities (24). This was in line with the resectability rate (5.6%) in our study sample. However, a systematic review by Sotiropoulos et al. revealed an overall resectability rate of 30% (28). Such a significantly low resectability rate in our study setting could be explained by the late presentation of patients to the tertiary facilities.

Limitations

The inherent limitation of the descriptive design employed is the failure to assess the factors that influenced the treatment options and their outcomes. Further analytical studies assessing both in-patients and out-patients need to be performed so as to address this limitation.

Conclusion

This study summarizes the sociodemographic and clinical characteristics of in-patients treated for HCC in a tertiary care hospital. Findings reveal a high proportion of late-stage diseases among participants that could have resulted in the observed low resectability rate.

Initiatives to facilitate the identification of the disease at an early stage are paramount. Screening programs have to target at-risk populations so as to facilitate early tumor detection and subsequent provision of curative treatment in order to improve overall survival. Proactive initiatives to introduce the liver transplant program as one of the curative options for HCC need to be done, as liver transplant is an optimal treatment option for a subset of patients with initial-stage disease. Lastly, Hepatitis B surveillance and vaccination programs need to be initiated so as to respectively treat and avoid this prevalent potential risk factor for developing HCC observed in the sample population.

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