Epidemiology, Clinico-radiological Profile and Management of Hepatocellular Carcinoma in a Tertiary Care Center in Nepal

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ABSTRACT

Introduction: Hepatocellular Carcinoma (HCC) is a common malignancy of gastrointestinal tract presenting in clinical practice. The common etiologies are hepatitis B virus (HBV), hepatitis C virus (HCV) and alcohol consumption. Treatment of HCC is multimodality based on Barcelona Clinic Liver Cancer (BCLC) staging system. The aim of the article is to study the demographic, clinico-radiological profile and treatment patterns of HCC patients.

Methods: This is a retrospective cross sectional study of patients diagnosed as HCC at Shree Birendra Hospital, Chhauni, Kathmandu, Nepal from April 2017 to March 2020. The study was approved by Institutional Review Committee. Data were collected for demography, clinical feature, histology, HBsAg status, serum AFP values, radiological findings and treatment details from hospital record. Data were analysed using Excel 2010 and SPSS v 21.

Results: Total of 36 patients diagnosed with HCC were included for analysis. There was a male predominance (72.22%) and the mean age was 66.75 ± 12.02 years. Pain abdomen and jaundice were present in 63.89% and 38.89% respectively at presentation and features of chronic liver disease (CLD) were evident in 83.33%. HBsAg was present in 44.44% of HCC. Location of tumour was primarily in right lobe (80.56%) and size of lesion varied greatly. Tissue diagnosis was obtained in 52.78% patients. Chemotherapy option was limited to Sorafenib.

Conclusions: HCC is more prevalent in older males. The common modes of presentation were pain abdomen and jaundice. Most of the HCC had underlying CLD and were advanced. Sorafenib was the mainstay of treatment in advanced HCC.

Key words: Hepatitis B; Hepatocellular carcinoma; Sorafenib

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DOI: 10.3126/mjsbh.v20i1.32256

Submitted on: 2020-10-18

Accepted on: 2021-01-09

INTRODUCTION

Hepatocellular Carcinoma (HCC) is the fifth most common cancer in the world and the third cause of cancer associated mortality as estimated by the World Health Organisation.[1] The annual incidence rates in Eastern Asia and Sub−Saharan Africa exceed 15 per 100,000 inhabitants.[2] The incidence ranges from four cases per 1,00,000 populations in USA to 150 cases per 1,00,000 populations in parts of Africa and Asia where HCC is responsible for a large proportion of cancer deaths. A rise in the incidence of mortality from HCC has been observed in different countries.[2] Eighty percent of all HCCs occurring in India occur with cirrhosis of liver in the background and 60% of all them are hepatitis B positive carriers. The estimated number of cases per year in India is approximately close to 22,000.[2] Nepal, however has low incidence for HCC owing to low prevalence for hepatitis B virus (HBV) and hepatitis C virus (HCV) infections.[3] Based on currently available data, crude incidence of liver cancer in Nepal is 0.9 and 0.8 per 1,00,000 in men and women respectively.[3] Management and treatment of patients with HCC varies according to various factors which include patient factors, socioeconomic factors, etiological as well as the disease status. Majority of the patients are treated with palliative and supportive care and life span is generally limited.[4]

Treatment of HCC is multimodality based on Barcelona Clinic Liver Cancer (BCLC) staging system and includes resection, liver transplant, local ablation, chemoembolisation and systemic therapy.[5] Sorafenib emerged as the first effective systemic treatment in HCC after 30 years of research, and is currently the standard-of-care for patients with advanced tumours.[5] In Nepal, majority of patients present late, thus most of them are treated with multikinase inhibitor Sorafenib or best supportive care.[3] In Nepal, nearly 15 to 20% of cases of HCC qualify for curative therapy including local ablation, resection, or transplant. Thirty five to forty percent patients present with locally advanced disease, making them eligible for loco-regional therapy or targeted therapy. In rest (40–50%) of the cases, presentation is usually at advanced stage (BCLC-D), and supportive therapy is all that can be offered at that point of time.[3] In recent advances in the treatment of HCC, check point inhibitors are at the forefront. Several other therapeutics such as inhibitory cytokine blockade, oncolytic viruses, adoptive cellular therapies and vaccines are also promising.[6] However, in a resource limited set up like ours, the present situation in regards to malignancies is not as optimum as it should have been. This study analyses the epidemiology, clinico-radiological profile and the management spectrum of HCC in a tertiary care hospital of Nepal.

METHODS

This is a retrospective cross sectional study of patients diagnosed as HCC attending Shree Birendra Hospital (SBH), Chhauni, Kathmandu, Nepal. SBH is a 635 bedded tertiary care hospital at Kathmandu, Nepal and is dedicated for treatment of all medical specialties for the beneficiaries of Nepalese defense personnel. The study was approved by Institutional Review Committee of our institute. Data were collected from Oncology Unit registry. Data of patients diagnosed with HCC were collected from April 2017 to March 2020. All patients diagnosed with HCC during this three year period were included in the study. Total number of patients included in the study was 36. Those patients whose diagnosis were uncertain or had inadequate records were excluded. Diagnosis of HCC was based on primarily triple phase CT scan, serum AFT level and tissues diagnosis as indicated. Staging was done using Barcelona Clinic Liver Cancer (BCLC) staging system.[5] Demographic profile, clinical features, histology, HBsAg status, serum AFP values, radiological findings and treatment details were duly collected. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as numbers and frequencies. Data was entered and analyzed using Excel 2010 and SPSS v 21.

RESULTS

Total 36 patients diagnosed with HCC were included for in the study for analysis. There was a male preponderance with 72.22%. The baseline characteristics of the study population are shown in Table 1. Presenting complaints of most of the patients were pain abdomen. Among the study subjects, total 23 (63.89%) patients presented with pain abdomen. Few patients presented with abdominal distention and ascites. Jaundice was

Table 1. Baseline characteristic of the study

Parameters		Values
Age in years (Mean ± SD)		66.75 ± 12.02
Male		26 (72.22%)
Age group distribution (years)	≤ 40	1 (2.78%)
	41 to 50	2 (5.56%)
	51 to 60	6 (16.67%)
	61 to 70	14 (38.89%)
	71 to 80	7 (19.44%)
	> 80	6 (16.67%)
Clinical features	Pain abdomen	23 (63.89%)
	Jaundice	14 (38.89%)
Serum APF values	Upto 50	15 (41.67%)
	51 - 400	8 (22.22%)
	401 - 1000	5 (13.89%)
	>1000	8 (22.22%)
HBsAg reactive		16 (44.44%)

seen in 14 (38.89) patients at presentation. HBsAg was done for all patients and 16 (44.44%) were HBsAg positive. Anti HCV testing reports were available for 13 patients only and none were positive.

All patients had triple phase CT scan of the abdomen and the summary of the radiological findings are presented in Table 2. Location of tumour was primarily on right lobe 29 (80.56%) and two patients had tumours in both lobes. Thirteen (36.11%) patients had single tumour while 23 (63.89%) patients had multifocal tumour. Size of lesion varied greatly with smallest being 1.8 cm x 1.8 cm x 1.2 cm and largest measuring 18.1 cm x 12.4 cm x 11.2 cm. Local regional lymph nodes involvement was seen in eight (22.25%) cases. They included periportal, paraaortic, portocaval, aortocaval, porta hepatis, mesenteric, peripancreatic, retroperitoneal lymph nodes of varying degree in sizes. Portal vein thrombosis was seen in four (11.11%) patients. Evidence of cirrhosis was seen in 30 (83.33%) patients.

The staging of patients at presentation as per BCLC staging system is shown in Table 3. There were no patients in very early stage (0) and early stage

Table 2. Radiological profile of the HCC (Mean ± SD in mm)

Parameters		Frequencies
Location of tumor	Right lobe	29 (80.56%)
	Left lobe	5 (13.89%)
	Both lobes	2 (5.56%)
Number of tumors	Solitary	13 (36.11%)
	Multifocal	23 (63.89%)
Regional lymph nodes involvement		8 (22.22%)
Portal vein invasion		4 (11.11%)
Evidence of cirrhosis		30 (83.33%)

while patients in intermediate stage (B) was 17.65%, advanced stage (C) was 61.76% and terminal stage was 20.59%.

Tissue diagnosis was obtained in 19 (52.78%) patients and microscopy showed hepatocellular carcinoma or poorly differentiated carcinoma consistent with hepatocellular carcinoma. Tissue diagnosis was not obtained when serum AFP values and triple phase CT scan was consistent with diagnosis of HCC.

Of the six patients in BCLC intermediate stage (B), only two patients received local therapy with TACE. All patients in BCLC advanced stage (C) received Sorafenib while patients in BCLC terminal stage (D) received best supportive care only. There were no patients in BCLC very early stage (0) and BCLC early stage (1), thus none were eligible for curative resection or liver transplantation.

DISCUSSION

In our study, the incidence increased from age of 50 years onwards and peak incidence was seen in 61 to

Table 3. Staging at presentation as per BCLC staging system

Very early stage (0)	Early stage (A)	Intermediate stage (B)	Advanced stage (C)	Terminal stage (D)
0	0	6 (16.67%)	23 (63.89%)	7 (19.44%)

70 years age group. In a study done in this region in the past, HCC occurrence was shown in two peaks, one at a young age between 40 to 55 years and another above 60 years.[4] These two peaks occur because of acquiring hepatitis B either in utero or in childhood, or exposure in adulthood. There was a male preponderance in our study which is approximately 2.6:1. The male preponderance as shown in our study has been demonstrated worldwide. Globally, the rate of men suffering from HCC is higher than women. The male to female ratio globally ranges between 2:1 and 4:1, with the difference being much predominant in high-risk areas.[7]

Presenting complaints of most of the patients were pain abdomen in our study. Few patients presented with abdominal distention and ascites, along with pain. The classic features of HCC include right upper quadrant pain. Weight loss, generalised weakness, abdominal swelling, non-specific gastrointestinal symptoms, and jaundice are other presenting features. Physical findings vary according to the stage of the disease. Ascites is often found, most commonly as a result of the underlying cirrhosis leading to portal hypertension, but rarely due to tumour spread to the peritoneum.[8]

In this study, 44.44% patients were HBsAg positive. In a similar study, infection due to HBV was 59% while HCV infection was seen in 15% patients.[9] In India, 70% to 80% of all HCCs are related to the hepatitis B virus (HBV), approximately 15% are related to hepatitis C virus (HCV), and 5% to both HBV and HCV. Alcohol alone accounts for approximately 8% of all HCC.[4] HCV RNA positivity and heavy alcohol use significantly increased the risk of HCC among cirrhotic patients, but not non-cirrhotic patients.[10] In a German study, HCC-patients with documented status on HCV / HBV-infection had HCV antibodies in 53% and HBs-Ag in 20%.[11] Another German study showed 25 (29%) of 85 patients were HBsAg or anti HBc positive, 21/85 (25%) were anti HCV positive, and 6/85 (7%) were positive for both HBV and HCV-markers.[12]

The treatment options for HCC depend on the cancer stage, patient performance status, and liver function and require a multidisciplinary approach based on Barcelona Clinic Liver Cancer (BCLC) staging system. The treatment modality include resection, liver transplant, local ablation, chemo-embolization and systemic therapy for the best patient outcomes.[5,11]

The multikinase inhibitor Sorafenib is the only approved targeted agent for advanced HCC presently. However, promising results have been obtained with other targeted agents and combinations too. Various ongoing trials may highlight the new therapeutic agents for HCC in the future.[13] Surgery is also an important modality for the management of HCC patients. However, in our study, surgery was not an option in any of our patients as most of our patients had presented during the advanced stage of the disease. Two out of six patients presenting in BCLC intermediate stage received local therapy in form of trans-arterial chemoembolization (TACE). Treatment of advanced hepatocellular carcinoma is the systemic therapy. As published by SHARP Investigators Study Group in 2008, in patients with advanced hepatocellular carcinoma, median survival and the time to radiologic progression were nearly three months longer for patients treated with Sorafenib than for those given placebo.[14] Majority of our patients were BCLC advanced stage and were thus treated with Sorafenib. One of our patients received immunotherapy with Durvalumab + Bevacizumab. Chemotherapy option was limited to Sorafenib only due to unavailability of other potential drugs in our country.

Aberrant activation of different signalling pathways as detected by molecular studies of HCC represent key targets for novel molecular therapies. At present for patients with advanced disease, Sorafenib is the only approved therapy although novel targeted agents and their combinations are emerging.[15] Clinical trials recruiting patients for treatment with immunotherapy to a combination of CTLA-4 inhibitor Tremelimumab and PD-L1 inhibitor Durvalumab versus Sorafenib has already shown positive results in advanced HCC patients.[6]

In a long term follow up study in Iran, the five year survival rate was estimated 19 (8.37%).[16] Average follow-up in this study was 14.3 months. Cox regression analysis revealed that the tumour size > 3 cm, involved lymph nodes > 2, combination

therapy with surgery and chemotherapy, and co-infection with hepatitis B virus and hepatitis C virus were the most relevant prognostic factors with five year survival rate in patients with HCC.[16] We could not do survival analysis as most of the patients were lost to follow up. Although our study was done in a tertiary care centre of Nepal Army, it is a single centric study and the results may not be applicable to the entire population. Our study had limited number of patients. Due to the unavailability of various promising drugs, we could not compare the efficacy of various chemotherapeutic agents in our study. We hope that our study would pave the way for further elaborate multi centric studies in the future for the benefit of HCC patients in the future.

CONCLUSIONS

HCC was more common in older males in our centre. Pain abdomen and jaundice were common modes of presentation. Most of the HCC patients had underlying CLD. Hepatitis B is important risk factors for HCC in our country. Most of the patients had advanced tumour as they presented late and Sorafenib was the mainstay of treatment in most of them. Prospective studies with larger sample size are necessary to further characterise the HCC in our country.

To cite this article: Deo RK, Chitalkar P, Malla S, KC I, Karki B, Thapa R. Epidemiology, Clinico-radiological profile and management of hepatocellular carcinoma in a tertiary care center in Nepal. MJSBH. 2021;20(1):6-11.

Conflict of Interest: None declared

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