Original Article

Indian Journal of Cancer Education and Research
Volume 5 Number 1, January - June 2017
DOI: http://dx.doi.org/10.21088/ijcer.2321.9815.5117.5

Clinical Profile and Therapy of Hepatocelluar Carcinoma at a Tertiary Care Institute from South India: A Retrospective Study of 182 Patients

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Received on 31.03.2017, **Accepted on** 04.04.2017

Abstract

Objective: To study the clinical profile and therapy of hepatocellular carcinoma (HCC) at a tertiary care institute in Andhrapradesh, Southindia. *Methods*: Data analysis of HCC patients enrolled in between 2000 and 2015. HCC was diagnosed according to EASL criteria-USG/CT/MRI of the abdomen and/or serum alpha-fetoprotein and/or histology (where indicated). Barcelona Clinic Liver Cancer (BCLC) staging was done. *Results:* We registered 182 HCC patients [males 162 (89%), mean age 57.5 ± 12.1 years]. An "Early Peak" (17%) was detected in 28-40 yr age group. The etiology of HCC was: Hepatitis B virus 70 (35.7%), Hepatitis C virus 05 (2.74%). Serum α-fetoprotein was >500 ng/ml in 43.8% and very high (>5000-100 000) in 30.6%. Classical features on triple phase CT in 80% with an average tumor size of (7.3 ± 2.1 cm), Portal vein invasion was seen in 40% and distant metastases in 11%. Majority of the patients (79.6%) were BCLC stage C and D. Biochemical: Thrombocytopenia (60%), anaemia in 30%, and 80% had an elevated alkaline phosphatase levels. Therapy was offered to 127 (69.78%) patients.Treatment given was as follows: Surgical resection (n=36 19.78%); Chemotherapy, both oral and iv (n=91 19.78%), and Sorafenib (n=36 19.78%), Best supportive care (n=55 30.22%), but survival data was not available due to lack of adequate followup. *Conclusions:* Hepatitis B infection is the predominant cause for HCC. Diagnostic range serum α-fetoprotein was detected in only 43.8% of study patients but its level correlates well with the disease burden, outcome. An "Early Peak" was observed in 28-40 year age group. Majority of the patients present with advanced disease, precluding the curative therapies. Universal immunization with hepatitis B vaccination will reduce the HBV infection rates & in part HCC burden in near future.

Keywords: HCC (Hepatocellular Carcinoma); AFP (Alpha Fetoprotein); HBV (Hepatitis B Virus).

Introduction

Hepatocellular cancer in adult men is the fifth most frequently diagnosed cancer worldwide, and is the second leading cause of cancer-related death in the world [1]. In adult women,it is the seventh most commonly diagnosed cancer and the sixth leading cause of cancer death [1]. The number of deaths per year in HCC is virtually identical to the incidence throughout the world, underscoring the high case fatality rate of this aggressive disease [1]. Hepatocellular carcinoma (HCC) results in between 250,000 and one million deaths globally per annum [2]. HCC has unique geographic, sex, and age distributions.The incidence of HCC varies widely according to geographic location [1]. The distribution of HCC also differs among racial and ethnic groups within the same country and between regions within the same country [3]. There is a paucity of data pertaining to the clinical profile, etiology, therapy of HCC patients in India, and especially from south india. Such information may be important to formulate guidelines for early detection and treatment of HCC in this country. This study was designed to provide the detailed clinical profile including clinical presentation, etiology (Hepatitis virus B,C) & biochemical, radiological profile along with serum AFP levels and therapeutic data of HCC at a tertiary care hospital in Andhra pradesh from South India.

Methods

Patients of hepatocellular carcinoma presenting to the sri venkateswara institute of medical sciences, a tertiary care center in Andhrapradesh from south india,between 2000 and 2015, were included in the study.

Study Design

Retrospective chart review of 182 patients diagnosed of HCC. Data was collected by review of medical records manually, which included admission and discharge notes and all medical reports, treatment.

Inclusion Criteria

All medical records of HCC with proper documentation and diagnostic, therapeutic information.

Exclusion Criteria Included

Significant unavailability of information in the charts, lack of reference to HCC etiology and absence of clinical and laboratory information in medical charts, patients referred from external institutions exclusively for treatment and patients lost to follow-up. HCC was diagnosed according to EASL criteria-USG/CT/MRI of the abdomen and/or serum α-fetoprotein and/or histology (where indicated). Detailed clinical and laboratory parameters were noted. Barcelona Clinic Liver Cancer (BCLC) staging was done. The following variables were used for the analysis:age and sex of the patient,modality of HCC diagnosis,viral etiology (Hepatitis B,C) and Performance status,BCLC stage, radiological and biochemical profile, serum a-fetoprotein (AFP) level (ng/mL) at diagnosis, evidence of distant metastases at diagnosis, locoregional and systemic treatment.

Statistical Analysis

This study was an exploratory observational analysis of the demographic data using SPSS Software linking.

Results

A total of 182 patients with HCC were registered for analysis.

Demographic Profile and Clinical Features

The mean age at presentation was 57.5 ± 12.1 years (range 28-87 years) and 162 (89%) of them were males and a small peak (17%) was detected in the age group of 28-40 years (Table 1). Pain abdomen in the right upper quadrant was the predominant symptom in 78% of the patients. Pain abdomen associated with loss of appetite was the main complaint in 49.4%, while none of them were asymptomatic (Table 1).

Table 1: Demographic profile and Clinical features of HCC patients (n=182)

Characteristic	Frequency	%
Age, years		
Mean	57.5 ± 12.1	
Range	28-87	
Small Peak (28-40 yrs)	31	17
Sex, n		
Male	162	89
Female	20	11
Predominant symptom, n		
Pain abdomen	142	78.0
Loss of appetite	21	11.5
Ascites	4	2.1
Lump	5	2.7
Fever	4	2.1
Hematemesis	2	1.0
Fatigue	2	1.0
Weight loss	2	1.0
Asymptomatic	0	0.0
Pain abdomen + LOA	90	49.4
Pain abdomen+LOA+LOW	52	28.5
Pain abdomen +Ascites	21	11.5
Pain abdomen +Fever	14	7.6

Etiology

Hepatitis virus as an etiological agent was detected in 70 (38.4%) patients. Of these, HBV alone was the causative agent in 65 (35.7%) and HCV accounting for only 5 cases (2.74%) (Table 2).

Tumor Characteristics

Serum AFP level was elevated in (77.5%,76/98 cases) & more than 500 units was detected in (43.8%, 43/98 cases) which is practically diagnostic of HCC [4] and significantly high level (>5000 –1,00,000 units) was observed in (30.6%, 30/98 cases) & normal range seen in (22%,22/98 cases) (Table 3). Most of the patients presented with advanced disease (79.6%). Radiological profile showed classical features of HCC on triple phase CT abdomen in (80%, 80/100 cases) in whom it was available with an average tumor size of 7.3 ± 2.1 cm and portal vein invasion seen in 40%. Biochemical profile showed 80% of patients had an elevated ALP levels, 50% with high normal total leucocyte count, 60% showed low normal platelet count and 30% had low Hb. The majority of the patients were in BCLC stage C and higher. Only 36 (20.5%) were in BCLC stage B and none of them were in BCLC stage A in which surgery could be considered (Table 3).

Therapy

Out of the 182 patients included, BCLC stage A,B,C and D was seen in 0, 20.3, 68.6 and 11%, respectively. Therapy could be offered to a total of 127 (69.78%) patients. The remaining 55 patients (30.22%) could not be offered any therapy due to factors such as advanced disease, poor performance status,non affordability or refusal of treatment.

Regarding treatment, 19.78% of patients (36/182 cases) underwent surgery, 50% (91/182 cases) recieved oral/iv chemotherapy, 30.22% (55/182 cases) of patients recieved best supportive care (Table 4). Approximately 20% (36/182 cases) of them received sorafenib and showed promising results despite few drug interruptions/dose reductions related to toxicity. Survival data was not available due to lack of adequate followup.

Early Peak

Small peak (17%, 31/182) was detected in the age group of 28-40yrs and it showed strong association with Viral etiology (1:2), whereas poor PS (PS-3) showed an effect in comparision to total population (p=0.0387) (Table 5).

Table 2: Hepatitis Virus association with HCC (n=182)

Etiology	Frequency	%
Hepatitis Virus	70	38.4
Hepatitis B Virus	65	35.7
Hepatitis C Virus	05	2.74

Table 3: Tumor characteristics

Characteristic	Frequency	%
AFP, ng/ml (n=98)		
<10	22	22.4
10-500	33	33.6
>500	43	43.8
>5000-1lakh	30	30.6
Radiological profile (n=100) Classical Triple	80	80
phase CT Average tumor size	7.3 + 2.1 cm	
Portal vein invasion	40	40
Biochemical profile (n=182)		
Elevated ALP level	145	80
High normal TLC	91	50
Low normal pl. count	109	60
Low Hemoglobin	55	30
Distant Metastasis (n=182)	20	11
BCLC staging (n=182)		
A	0	0
B	37	20.3
C	125	68.7
D	20	11
BCLC = Barcelona clinic liver cancer		

Table 4: Modalities of therapy (n=182)

Treatment	Patients	%
Surgical resection	36	19.78
Oral+IV chemotherapy	91	50
Best supportive care	55	30.22
Sorafenib	36	19.78

Table 5: Early peak (28-40 yrs) vs Total population (n=182)

Incidence	Early Peak N (%)	Total Population N (%)
No of patients	31 (17)	182 (100)
Viral etiology	16 (51.6)	70 (38.4)
Diagnostic AFP	10 (32.2)	43/98 (43.8)
Advanced disease	20 (64.5)	145 (79.6)
Best supportive care	11 (35.5)	55 (30.2)
Poor PS (PS 3)	11 (35.5)	35 (19.2)

AFP=alpha-fetoprotein PS=Performance status

Discussion

This comprehensive study of HCC from a tertiary care institute in Andhrapradesh, Southindia is the first of its kind to provide the demographic profile, clinical features, etiology, tumor characteristics, BCLC Staging and the modalities of various therapies over a relatively long period of time in a developing country with intermediate endemicity for HCC [5].

The mean age of the patients in our study was 57.5 years which is similar to an earliest series from india [6]. Several large prospective studies conducted in both Asia and Western Europe have noted a mean age at presentation between 50-60 years [7-9]. A small peak was detected in this study in the age group of 28-40 yrs which was not seen in previous indian studies. In some regions, the age of diagnosis of HCC is decreasing like for example in sub Saharan Africa the mean age of presentation is 33 years [10]. This Early Peak showed a strong asscociation with viral etiology (1:2), whereas poor PS (PS-3) showed an effect in comparision to total population (p=0.0387). The younger age of HCC patients with HBV infection can be explained by 2 facts. First, the HBV carrier pool in India usually reaches a plateau by the age of 5 years [11,12]. In the general population, it is estimated that about 75% carriers would have acquired infection by horizontal spread during early childhood and about 25% by vertical transmission [13]. Second, HBV is a more potent oncogenic stimulus and can cause HCC without cirrhosis [14].

The strong male predominance in our study (the male to female ratio was 8:1) was similar to the global trend [15]. In all parts of the world, men are more likely than women to develop HCC [16]. The disparity is more pronounced in high-incidence regions, where men are affected 2.1 to 5.7 times more frequently than women (mean 3.7:1) per 100 000 persons. The ratio decreases to a mean of 2.4:1 in intermediate-incidence areas like Asia [16].

Infection due to HBV (35.7%) emerged as the single most factor associated with HCC. This is consistent with other studies from the Indian subcontinent [17,18,19]. As per the literature almost 80 percent of cases are due to underlying chronic hepatitis B and C virus infection [20]. The carrier rate of HBV reported from India is 2-4% [21]. Approximately 40 million HBV carriers exist in India,comprising 10% of the global burden. HCV infection was seen in only 5 (2.74%) patients and it was very low compared to the studies from other parts of india [22,23]. In India, the prevalence of HCV is about 0.8-1.5% of the general population and it has been implicated as the causative agent in 14-26% of chronic liver disease in india [24,25]. Thus, HBV is a much more important carcinogen in Indian patients than in the West,where alcohol and HCV are the leading etiological agents.

The major complaint of our patients with HCC was abdominal pain,which was seen in more than 75% followed by loss of appetite. The most common symptomatology observed was pain abdomen associated with loss of appetite seen in 90 (49.4%) patients and pain abdomen with associated loss of appetite, weight loss was seen 52 (28.5%). Our previous studies has highlighted the importance of symptomatology (weight loss, anorexia and abdominal pain) as markers for HCC [26]. Interesting thing noted was none of the patients were asymptomatic indicating the advanced nature of the disease at presentation.

Serum AFP level >500 ng/ml is taken as a conventional diagnostic level for HCC [27]. In this study, AFP was elevated in 77.5% of patients, but

was above the diagnostic range in only 43.8% of patients. One important finding noted in this study was, about 30.6% of patients found to have highly significant elevated AFP levels (>5000-100 000 ng/ml) which was not reported in previous studies from india. Low serum levels may be either because of smaller tumors or due to better differentiation of masses that do not produce high AFP [28]. The level of AFP did not show any correlation to the etiology of HCC whereas (96.67%) of patients who had AFP levels (>5000 – 100 000 ng/ml) found to have advanced disease at presentation indicating the burden of disease and only (13.33%) of them were received curative therapies resulting in probably poor outcomes. Despite the issues inherent in using AFP for the diagnosis of HCC, it has emerged as an important prognostic marker, especially in patients undergoing resection and those being considered for liver transplantation. Patients with AFP levels >1000 ng/ml have an extremely high risk of recurrent disease following transplantation, irrespective of the tumor size [29,30].

Radiological profile showed classical features (Arterial enhancement, Delayed washout) of HCC on triple phase CT abdomen in (80%, 80/100 cases) in whom it was available with an average tumor size of 7.3 ± 2.1 cm and portal vein invasion seen in 40%. These findings are in consistent with the literature where the arterial phase of enhancement allows for detection of hypervascular HCCs as small as 3mm and addition of delayed phase imaging improves detection of these tumors [31] with a sensitivity and specificity of more than 90% [32]. The previous studies from india had almost similar findings [33,34].

Biochemical profile showed 80% of patients had an elevated ALP levels, 50% with high normal total leucocyte count, 60% showed low normal platelet count and 30% had low Hb. Laboratory examination is usually nonspecific. The majority of patients who develop HCC may have thrombocytopenia, anaemia and abnormal alkaline phosphatase levels indicating the severity of liver dysfunction [35].

Almost 80% of the patients had advanced disease at initial presentation which is similar to the Indian data [36]. 20 patients (11%) found to have distant metastasis at initial presentation. Extrahepatic spread is present at the time of diagnosis in only approximately 5 to 15 percent of cases according to literature [37,38], same was reflected in this study.

The majority of the HCC patients reporting to our hospital were in BCLC stages C and B [125 (68.7%) and 37 (20.3%), respectively] and remaining patients (11%) had BCLC stage D, all of these were symptomatic at their first presentation, suggesting advanced disease to begin with. On account of this, only 127/182 patients (69.78%) could be offered treatment. This observation is quite consistent with other reports from the country [39,40,41].

Only 36 (19.78%) patients in the present series underwent hepatectomy and none underwent liver transplantation, which was almost similar as reported in previous studies [42]. In India, living donor liver transplantation is still at the nascent stage. Cadaveric liver transplantation is limited by shortage of donors and prolonged waiting periods. Additionally, the procedure is very expensive and, with no health insurance facilities available and severe economic constraints, it is virtually out of reach for the majority of the patients in India. Additionally, since most of our patients were in BCLC stages C and D, this precluded surgical therapies.

Though there is no standard therapy for patients with advanced tumors who are not considered for any locoregional treatments, we used various systemic chemotherapeutic regimens, such as 5-FU, Cisplatin, Mitoxantrone, Cyclophosphamide, Thalidomide and Oral Etoposide, Capecitabine in our patients. A preliminary study has suggested that sorafenib, an oral multikinase inhibitor of the vascular endothelial growth factor receptor, the platelet-derived growth factor receptor, and Raf, may be effective in HCC. When used in advanced HCC, median survival and the time to radiologic progression was nearly 3 months longer for patients treated with sorafenib than for those given a placebo [43]. Only 36 (19.78%) patients were received Sorafenib due to poor affordability and showed promising results despite few drug interruptions/dose reductions related to toxicity. Survival data was not available due to lack of adequate followup.

Based on this study we can see the regional burden and epidemiological data concerning HCC patients at a tertiary care institute in Andhra pradesh, Southindia.

Conclusion

Hepatitis B infection is the predominant cause for HCC. Diagnostic range serum α-fetoprotein was detected in only 43.8% of study patients but its level correlates well with the disease burden, outcome. An "Early Peak" was observed in 28-40 year age group. Majority of the patients present with advanced disease, precluding the curative therapies. Universal immunization with hepatitis B vaccination will reduce the HBV infection rates & in part HCC burden in near future.

Acknowledgments

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