Clinical Profile, Etiology and Therapeutic Outcome in 324 Hepatocellular Carcinoma Patients at a Tertiary Care Center in India

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Key Words

Hepatocellular carcinoma · India · Serum α -fetoprotein · Etiology · Staging · Treatment

Abstract

Objective: To study the profile and outcome of therapy for hepatocellular carcinoma (HCC) in India. **Methods:** Data analysis of HCC patients enrolled in liver clinic between 1990 and 2005. **Results:** We registered 324 HCC patients [males 284 (88%), mean age 52.4 ± 13.1 years]. The etiology of HCC was: hepatitis B virus 165 (51%), hepatitis C virus 38 (12%), alcohol 20 (6%), combined 31 (10%) and unknown 70 (21%). Serum α -fetoprotein was >400 ng in 36%, portal vein invasion was seen in 40% and distant metastases in 13%. Therapy was offered to 141 (43.5%) patients, but survival data was available in only 130 (93%) of them. Treatment given and median survival time was as follows: surgical resection, 19 months ($n = 14$); transarterial chemoembolization, 11 months ($n = 23$); transarterial rehemium therapy, 26 months ($n = 7$); radiofrequency ablation, 24 months ($n = 4$); acetic acid ablation, 13 months ($n = 17$); oral chemotherapy, 26 months ($n = 33$), and combination therapy, 26 months ($n = 32$). Vascular invasion, Okuda staging and therapy were independent factors associated with survival. Treated patients had longer median survival compared to untreated ones (16 months vs. 7 months, $p < 0.05$). **Conclusions:** Hepatitis B infection is the predomi-

nant cause of HCC in India. Serum α -fetoprotein was diagnostic in only one third of our patients. Most patients present late, when curative therapies are not possible. Treated patients had better survival than untreated ones.

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Introduction

The burden of hepatocellular carcinoma (HCC) is increasing and at present HCC is ranked as the fifth most common cancer worldwide [1]. The incidence of HCC varies widely with the geographic location as risk factors for the development are variably distributed across continents and within countries. Age-adjusted incidence rates for liver cancer in developing countries are 2- to 3-fold higher than in the developed countries [2]. Approximately 80% of liver cancers occur in Asia and Africa [3].

Existence of chronic liver disease, especially cirrhosis, represents a potential risk for the development of HCC. Cirrhosis, mainly caused by hepatitis B virus (HBV) and hepatitis C virus (HCV), constitutes a major risk factor for HCC, with a 5-year cumulative incidence ranging from 15–20% [4]. While HCV is the most common cause of HCC in the USA and Japan, HBV appears to be the most important etiological agent for HCC in southeast Asian countries, including China and Taiwan [5].

India lies in the intermediate endemic zone of HBV infection with hepatitis B surface antigen (HBsAg) carrier frequency of 2–4% in the community [6]. HBV infection is the leading cause of chronic liver disease in India and is responsible for 35–60% of chronic liver disease and 60–80% of HCC [5]. Earlier studies from India suggest that the odds ratio of HBsAg positivity among HCC patients is one of the highest in the world [7]. About 15 million people are infected by HCV and the population prevalence of anti-HCV antibodies is about 1% [8]. Thus, there is a large pool of people who are at risk of developing chronic liver disease and, therefore, HCC. Post-mortem studies from India show a prevalence of HCC varying from 0.2 to 1.6% [9]. A recently published prospective cohort study has revealed the incidence of HCC among Indian patients of cirrhosis as 1.6% per year [10].

There is a paucity of data pertaining to the clinical profile, etiology, outcome of therapy and survival of HCC patients in India. Such information in India may be important to formulate guidelines for early detection and treatment of HCC in this country. This study was designed to provide the clinical features, underlying risk factors, tumor characteristics and outcomes of therapy in HCC patients from India.

Methods

Patients of HCC presenting to the liver clinic of the All India Institute of Medical Sciences, a tertiary care center in India, between 1990 and 2005, were included in the study.

Study Design

Patients included were divided into 2 groups: group I included those who presented between 1990 and 2000, and group II contained those who presented between 2001 and 2005. For group I, the data were collected retrospectively from the case records, and for group II, data were accumulated by prospective follow-up from 2001 onwards. During the later period (2001–2005), screening services for HCC were started at the liver center of our institute.

Patient Evaluation

Clinical evaluation included detailed history and physical examination. Investigations included complete blood count, liver function tests and viral markers for HBV and HCV. Upper gastrointestinal endoscopy was done in each to detect the presence of esophageal varices. Serum α -fetoprotein (AFP) was estimated using a particle enzyme immunoassay (AxSYM System; Abbott Laboratories, Abbott Park, Ill., USA; normal range <20 ng/ml).

The hepatitis viral markers, including HBsAg (Organon Teknika, Boxtel, The Netherlands), anti-HCV (Xcyton, Bangalore, India), total anti-HBc and HBeAg (Bio-Rad, MonoLISA, France) were tested using commercial ELISA [11]. HBV DNA and

HCV RNA were first detected using qualitative PCR [12–14] and if they were positive, they were quantitated by in-house competitive PCR (CT-PCR) described earlier [14, 15]. The sensitivity of qualitative PCR for HBV DNA was 100 copies/ml, for HCV RNA 500 copies/ml [12, 13] and for CT-PCR it was 10^2 copies/ml [14, 15]. These tests were done at initial presentation and every 3 months thereafter in patients treated with antiviral drugs. Among patients positive for HBV infection, genotyping was performed in a random sample of HBV-induced HCC.

Radiological work-up comprised of an abdominal ultrasonogram and contrast-enhanced CT abdomen for patients of group I. For group II patients, a triple-phase CT (TPCT) of the liver was done at the time of enrolment. Contrast-enhanced multiphasic MRI was also done in this group when required for the diagnosis of HCC.

Diagnosis of cirrhosis was made on the basis of clinical, biochemical and endoscopic findings. Liver biopsy was done wherever necessary. HBV cirrhosis was diagnosed when detectable HBsAg in serum was present. HCV cirrhosis was diagnosed when detectable anti-HCV, HCV RNA or both was present in serum.

Alcoholic cirrhosis was labeled when the patient had a history of alcohol consumption of ≥ 80 g/day for more than 5 years. Severity of cirrhosis was graded based on the Child-Pugh classification [16].

Diagnostic criteria for HCC in group I were any of the following: AFP >300 ng/ml or hypervascular liver mass on contrast-enhanced CT abdomen or fine needle aspiration cytology (FNAC). For group II, the modified European Association for Study of Liver criteria [4] were followed. This consisted of either FNAC or any 2 of the following: AFP >300 ng/ml or arterialization of the mass on TPCT or MRI. MRI was performed at times to document arterial enhancement of lesion in patients who had arterial enhancement with TPCT, but did not have requisite raised AFP values and who had equivocal FNAC. Therefore, arterial enhancement on 2 imaging modalities could be achieved in these cases, satisfying the European Association criteria.

Staging of HCC was done according to the Barcelona Clinic Liver Cancer (BCLC) staging classification [17], retrospectively for group I and prospectively for group II.

Treatment

Various types of treatment therapies available at our center, were given keeping into account factors like stage of the disease, underlying presence of cirrhosis and its severity. Therefore, findings on CT and TPCT indicating tumor burden, portal vein involvement, presence of extra-hepatic disease or distant metastasis were recorded. Child's score and PST score of the patient was also noted and the treatment was then finally decided.

Locoregional Therapies

BCLC A stage patients were offered surgery if their liver function was good with no clinically relevant portal hypertension. If not, then surgery could not be undertaken, and instead local ablative therapies were performed. These local ablative therapies were radiofrequency ablation (RFA) or percutaneous acetic acid injection (PAI) and were undertaken at our center from 2001 onwards. RFA and PAI were done in those patients who had HCC ≤ 5 cm and ≤ 5 in number. The RFA technique being expensive, this treatment was offered only to those who could bear the cost of the needle electrode, failing which, PAI was undertaken as the thera-

Fig. 1. Radio frequency ablation. **a** Arterial phase of TPCT showing a solitary, peripherally located, enhancing HCC (arrow) in the liver. RFA was performed. **b** TPCT performed at 4 weeks shows the same mass as uniformly hypodense, larger than the pretreatment size and with no enhancing viable tissue, suggesting complete ablation.

Fig. 2. Percutaneous acetic acid injection (PAI). **a** Arterial phase of TPCT showing an enhancing, well defined HCC (arrow) in the left lobe of liver. After subjecting to PAI, TPCT done at 4 weeks (**b**) shows the same mass as uniformly hypodense with no enhancing viable tissue suggesting complete ablation.

peutic option. Patients having tumor close to the surface of liver without a rim of normal liver tissue around the tumor margin, near the diaphragm, major hepatic vessels and gall bladder were excluded from ablative therapy and the regional therapy of transarterial chemoembolization (TACE) was undertaken to avoid procedure-related complications. Other considerations were normal coagulation profile and absence of associated co-morbid illnesses.

Radiofrequency Ablation

The procedure was performed using a cool-tip RF system (Radionics, Burlington, Mass., USA) with continuous ice cold perfusion system. The procedure was done under local anesthesia and sedation. A single or cluster electrode (depending upon the size of the mass) was inserted into the mass using ultrasound guidance. The needle tract was cauterized by withdrawing the electrode while still hot. End temperature $>60^{\circ}\text{C}$ was achieved at the end of each session (fig. 1). Platelet-rich plasma was transfused if platelet count was $<50,000/\mu\text{l}$.

Percutaneous Acetic Acid Injection

Under local anesthesia using ultrasound guidance, 40% glacial acetic acid was injected into the mass through the percutaneous route using a 22 G spinal needle. Multiple sessions of PAI were performed and 1.5–2 ml was injected in 1 session per week (total dose not exceeding 3 times the diameter of the mass; fig. 2). To

minimize post-procedural pain, injection bupivacaine (Sensorcaine) was administered at a dose of 4–5 ml through the same needle into the tumor, needle track and the liver capsule while gently withdrawing the needle.

Transarterial Chemoembolization

Patients of BCLC stages B and C with patent main portal vein, with or without segmental or lobar portal vein invasion and who did not have extrahepatic disease were offered either transarterial rehenium therapy (TART) or TACE. The few cases of BCLC stage A which were unsuitable for ablation or surgery (not fulfilling the inclusion criteria for ablation) were also treated with TACE. The TACE procedure was carried out by preparing a stable drug mixture of doxorubicin 50 mg and cisplatin 100 mg in combination with 10–15 ml of ionic contrast media and 10–20 ml of lipiodol by continuously agitating the mixture. Superselective catheterization of the hepatic artery supplying the mass was performed through the femoral artery puncture in the upper thigh. Gelfoam particles were injected subsequent to institution of intra-arterial chemotherapy for embolization to occlude the artery supplying the mass (fig. 3a, b).

Transarterial Rehenium Therapy

A stable lipophilic chelate with rehenium, called ^{188}Re HDD-lipiodol, was prepared and 185 MBq (5 μCi) was initially injected through the 4/5 F preshaped catheter in the hepatic artery branch-

Fig. 3. TACE for local recurrence of HCC following surgery. A small, exophytic, local recurrence following surgery in segment 8 of liver on arterial phase MRI. **a** TACE was performed and follow up after TACE with arterial dominant CT. **b** Lipiodol completely covering the mass and the adjoining hepatic parenchyma with no enhancing residual tissue. Multiple para-esophageal collaterals are also seen.

Fig. 4. Combination modality (RFA followed by TACE). A small, solitary enhancing mass in segment 7 of liver on arterial phase CT (**a**), treated with RFA. At 18 months, multiple fresh lesions along with recurrence at the margin of the defect were noted and TACE was performed. Post-TACE CTs (**b**, **c**) show lipiodol-covered lesions. Straight arrows = fresh lesions; curved arrow = recurrence.

es after performing the femoral artery puncture in the upper thigh. Subsequently, whole-body imaging was performed under the gamma camera, after infusing the standard dose of Re-188-lipiodol (100 μ Ci) mixture via the femoral artery catheter. The radiation-absorbed dose was calculated for the lungs, whole liver and tumor only. This calculated dose was then injected through the catheter in the hepatic artery feeding the tumor.

Combination Therapy

A combination of different treatment modalities was used in some patients. The modalities used were RFA, TACE and PAI (fig. 4). This mode of therapy was chosen for a few of the BCLC stage A patients who changed to BCLC stage B/C on follow-up after therapy. Some patients of BCLC stage B/C who failed to respond favorably following TACE/TART were also subjected to combination therapy with ablation (either RFA or PAI) for the poorly responding index tumor.

Oral Chemotherapy

Two categories of patients of BCLC stage D were given oral chemotherapy: (1) advanced HCC patients having Child's A/B cirrhosis, with portal vein involvement and extrahepatic spread, Performance Status score 0–2, and (2) terminal stage HCC with Child's C cirrhosis, PST score >2 (therapy offered to those who could afford it while others were offered only symptomatic treatment).

Systemic oral chemotherapy with 5-fluorouracil, long-acting somatostatin or a combination of anti-angiogenic drugs and thalidomide along with capecitabine was given.

Adjuvant Therapy

All patients with cirrhosis who had evidence of high-risk varices on endoscopy underwent primary prophylaxis with endoscopic variceal banding. Patients who had HBV-related HCC along with markers of active viral replication were given antiviral treatment with oral lamivudine 100 mg daily. The other complications of chronic liver disease and HCC were managed with conventional treatment.

Follow-Up

All treated patients were followed up by detailed clinical examination, serum AFP and TPCT at 1, 3 and 6 months to assess the response. Thereafter, TPCT was done once a year. If CT showed residual or recurrent disease, the therapy allotted (TACE/RFA/PAI) was repeated provided the patient was found clinically fit with a Child's status of A/B. In certain situations where CT/TPCT showed no evidence of recurrence or fresh lesions following treatment, but the patient had rising serum AFP level, repeat TACE was undertaken. If there was progression of disease on follow-up imaging, then, depending upon the BCLC stage of the disease, other available treatment options were also considered. Hence, in patients treated with either TACE or RFA/PAI, single or multiple sessions were undertaken depending upon their response to therapy.

Statistical Analysis

Data analyses were performed using Stata (version 9.0). Continuous data were expressed as mean (SD) or median (range) and categorical data as proportions. Data for median survival were analyzed using Kaplan-Meier analysis, and survival difference among various groups was tested using the log-rank test. Cox regression analysis was used for assessing factors associated with survival. A *p* value <0.05 was considered significant.

Results

A total of 324 patients with HCC were registered in the liver clinic (50 in group I and 274 in group II).

Clinical Profile and Liver Function Status

The mean age at presentation was 52.4 ± 13.1 years (range 18–92 years) and 284 (88%) of them were males. Abdominal pain in the right upper quadrant was the predominant symptom in 53% of the patients (table 1). Recent onset ascites was the main complaint in 13%, while weight loss was present in 9% (table 1). Patients with HCC who were asymptomatic were diagnosed to have the disease during routine ultrasonographic evaluation for vague abdominal complaints. There was a past history suggestive of acute hepatitis in 34 (11%) and chronic hepatitis in 26 (8%) patients. History of significant intake of alcohol was present in 44 (14%) with a mean intake of 86 g/day and median duration of 17.5 years (range 0–40). The biochemical markers, Child's class and presence of esophageal varices are shown in table 2. Esophagoscopy revealed presence of esophageal varices in 134 (58%) patients.

Etiology

A significant proportion of our patients (316/324, 97.5%) had underlying cirrhosis.

Table 1. Demographic profile and clinical features of HCC patients (n = 324)

Characteristic	Frequency	%
Age, years		
Mean $\pm$ SD	52.4 $\pm$ 13.1	
Range	16–92	
Sex, n		
Male	284	88.0
Female	40	12.0
Predominant symptom, n		
Pain	174	53.2
Ascites	41	12.7
Weight loss	28	8.9
Fever	20	6.3
Lethargy	15	4.6
Lump	12	3.8
Asymptomatic	34	10.5
History of		
Acute hepatitis	34	11.0
Chronic hepatitis	26	8.0
Blood transfusion	23	7.0
Significant alcohol consumption		
Consuming $\geq$ 80 g/day, n	45	14.0
Quantity, g/day	86 $\pm$ 53	
Median duration (range), years	17.5 (0–40)	
Smokers, n	32	10.0

Table 2. Liver function tests, Child's class and endoscopic examination (n = 324)

Serum bilirubin, mg/dl	1.3 (0.2–26.3)
Serum albumin, g/dl	3.5 (1.6–9.8)
AST, U/l	87.5 (15–559)
ALT, U/l	58 (7–507)
SAP, U/l	330.5 (10–2,720)
Child's class	
A	165 (51)
B	110 (34)
C	49 (15)
Grade of varices (n = 232)	
No varices	98 (42.2)
1	11 (4.7)
2	75 (32.3)
3	38 (16.4)
4	10 (3.1)

Data are median (range) or n (%) as appropriate.

Table 3. Etiological factors associated with HCC (n = 324)

Etiology	n (%)
HBV	165 (50.9)
HCV	38 (11.7)
Alcohol	20 (6.1)
HBV + alcohol	17 (5.2)
HBV + HCV	7 (2.2)
HCV + alcohol	4 (1.2)
HBV + HCV + alcohol	3 (0.9)
Unknown	70 (21.6)

Table 4. Tumor characteristics

Characteristic	n (%)
AFP, ng/ml (n = 271)	
<10	77 (29)
10–400	93 (35)
>400	101 (36)
Size, cm (n = 313)	
<3	48 (16)
>3–5	54 (18)
>5	211 (67)
Number of lesions (n = 313)	
Solitary	215 (69)
2–3	48 (15)
4–5	15 (5)
>5	35 (11)
Portal vein thrombosis	129 (40)
Distant metastasis	41 (12.7)
Okuda staging (n = 313)	
1	100 (31.9)
2	169 (54)
3	44 (14.1)
BCLC staging (n = 292)	
A	60 (20.5)
B	101 (34.6)
C	80 (27.4)
D	51 (17.5)

BCLC = Barcelona Clinic Liver Cancer Staging.

HBV infection was the most common etiological factor and was detected in 192 (59%) patients. Of these, HBV alone was the causative agent in 165 (51%), and in the remaining patients, association with HCV and alcohol was present (table 3).

Of those patients who were HBeAg negative (n = 145), HBV DNA was positive in 18 (12%), qualifying as 'e mutants'. A HBV genotype analysis of 38 patients chosen at

Table 5. Modalities of therapy and survival

Treatment	Patients, n (%)	Survival	
		median	range
Surgical resection	14 (10.7)	19	1–28
RFA	4 (3.0)	24	2–30
PAI	17 (13.1)	13	1–51
TACE	23 (17.7)	11	1–41
TART	7 (5.4)	26	1–32
Oral chemotherapy	33 (25.3)	5	1–16
Combination therapy ¹	32 (24.6)	26	1–58
Total treated	130	16	1–58

¹ Two modalities in 29 patients and 3 modalities in 3 patients.

random revealed that 71% were genotype D, 21% genotype A and 8% were genotype C. However, the genotypic distribution among patients with HCC was similar to the genotypic distribution among other patients with HBV-induced chronic liver disease reported from our center and from other centers in this country [18, 19].

Comparison of HCC Based on Etiology

When comparing age, various biochemical variables and tumor characteristics based on various etiologies of HCC, only the mean age of HBV-related HCC was significantly lower than the HCV- and alcohol-related HCC (49.3 ± 11.8 years vs. 59.6 ± 11.3 vs. 56.1 ± 13.8 , $p < 0.05$). The mean bilirubin, albumin, aspartate transaminase and alanine transaminase levels did not reveal any significant difference. Serum AFP, tumor size and portal vein thrombosis also did not show statistical significance among the 3 major groups.

Tumor Characteristics

In 265 (85%) patients, the dominant lesion was more than 3 cm in size (table 4). There was a single lesion in 215 (69%) and >5 lesions in 35 (11%). Portal vein involvement was identified on imaging in 129 (40%). Extra-hepatic metastasis to peri-pancreatic nodes, celiac nodes, inferior vena cava thrombosis and lungs were seen in 41 (13%) of the patients. The median serum AFP value in the 271 patients in whom it was available was 350 ng/ml (range 0.72–2,771,360 ng/ml). The majority of the patients were in BCLC stage B and higher. Only 60 (20%) were in stage A, in which surgery could be considered. Another 51

Table 6. Cox regression analysis of various factors predicting survival

	Hazard ratio	p value	95% CI
Female	0.77	0.28	0.43–1.28
Etiology			
Unknown	1.0	–	–
HBV	0.84	0.46	0.54–1.33
HCV	0.88	0.70	0.46–1.68
Alcohol	1.97	0.07	0.95–4.10
Other ¹	1.71	0.12	0.86–3.41
Blood transfusion	0.93	0.84	0.43–1.99
Chronic hepatitis	1.10	0.43	0.71–1.70
Cirrhosis	1.03	0.87	0.72–1.47
Child's score			
A	1.00		
B	1.98	<0.001	1.35–2.90
C	2.36	<0.01	1.30–4.30
Diameter, cm			
<2	1.0	–	–
>2	1.55	0.05	0.99–2.41
Number of lesions			
1	1.0	–	–
>1	0.99	0.96	0.68–1.45
Distant metastases	1.66	0.04	1.04–2.65
Vascular involvement	2.12	<0.001	1.44–3.10
Okuda staging			
1	1.0	–	–
2	3.08	<0.001	2.00–4.75
3	4.67	<0.001	2.56–8.50
Any treatment	0.47	<0.001	0.33–0.69

¹ HBV + HCV, HBV + HCV + alcohol and HBV + alcohol.

(17.5%) of the patients were in stage D, where curative or palliative therapy could be offered.

Therapy and Outcome

Out of the 324 patients included, 50 were in group I while 274 were in group II. BCLC staging could be performed in 292 patients, and BCLC stage A, B, C and D was seen in 15, 35, 23 and 28%, respectively, in group I and 21, 35, 28 and 16% in group II. Therapy could be offered to a total of 141 (43.5%) patients [12 (24%) of group I and 129 (47%) of group II, $p < 0.01$]. The remaining 183 patients could not be offered any therapy due to factors such as advanced disease, non-affordability or refusal of treatment.

Survival data was available for 130 treated patients and 143 non-treated patients. Table 5 provides the details of therapy and the survival outcome.

Fig. 5. Kaplan-Meier analysis of patients in relation to treatment. Broken line = patients who did not receive treatment (n = 143); continuous line = patients who received treatment (n = 130; $p = 0.0000$, log-rank test).

Surgical resection was done in 14 patients (10.7%) with a median survival of 19 months. Percutaneous therapy was given to 21 patients (PAI in 17 and RFA in 4 patients, mean sessions 3.8 and 1, respectively), and the median survival was 13 and 24 months, respectively. TACE was offered to 23 patients (39 sessions) with a median survival of 11 months. TART (n = 7) and oral chemotherapy patients (n = 34) had a median survival of 26 and 5 months, respectively. Combined treatment [n = 32 (24.6%)] patients had a survival of 26 months.

Follow-up data were available in 273 patients, out of which 124 died while 149 survived. The mean follow-up was 7.4 ± 10.3 months (median 3 months). The median survival for all patients using Kaplan-Meier estimates was 11 months. The median survival for the treated and untreated group was 16 and 7 months, respectively ($p < 0.001$; fig. 5). Other individual variables, which showed significant survival on Kaplan-Meier estimates, were portal vein invasion, Child's class, BCLC, Cancer of the Liver Italian Program (CLIP) and Okuda staging. The Kaplan-Meier estimate for median survival in the absence of portal vein invasion was 15 months and in patients with invasion it was 6 months ($p = 0.0007$). When all the 3 major staging systems – BCLC, CLIP and Okuda – were put in a Cox's model in a stepwise manner, Okuda staging emerged as an independent predictor of survival. Child's score significantly correlated with survival: while it was 16 months in Child's A, it was only 6 months in Child's B and C ($p = 0.0002$).

There was no difference in survival in patients based on gender ($p = 0.28$) or serum AFP level ($p = 0.60$). Patients with alcohol-related HCC had poor survival when compared to viral causes of HCC, although this did not reach statistical significance ($p = 0.07$). On Cox's regression analysis, vascular invasion, distant metastasis, Child's class, diameter of tumor and Okuda staging were factors that were associated with survival. Age, sex, past history of chronic hepatitis, AFP or number of lesions did not predict survival (table 6).

Discussion

This comprehensive study of HCC from the Indian subcontinent is the first of its kind to provide the clinical features, etiology, tumor characteristics, underlying risk factors and the outcomes of various therapies over a relatively long period of time in a developing country with intermediate endemicity for HCC.

Almost all our patients (97.5%) had underlying cirrhosis, and infection due to HBV (59%) emerged as the single most factor associated with HCC. This is consistent with other studies from the Indian subcontinent [20–22]. The carrier rate of HBV reported from India is 2–4% [23]. Approximately 40 million HBV carriers exist in India, comprising 10% of the global burden.

HCV infection was seen in 48 (15%) patients. 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]. In 13.4% of our patients, alcohol has been found as either the sole etiologic agent or in combination with viral hepatitis. 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 mean age of the patients in our study was 52.4 years which is similar to an earlier series from India [20]. HBV-related HCC patients in our study presented a decade earlier when compared to HCV-infected HCC patients (49.3 vs. 59.6 years), which is comparable with earlier studies [26, 27]. 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 [28, 29]. 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 [30]. Second, HBV is a more potent oncogenic stimulus and can cause HCC without cirrhosis [31].

The majority of the HCC patients reporting to our hospital were in BCLC stages B and C [101 (34.6%) and 80 (27.4%), respectively] and about 89.5% of these were symptomatic at their first presentation, suggesting advanced disease to begin with. On account of this, only 141/324 patients (43.5%) could be offered treatment. This observation is quite consistent with other reports from the country [20, 22, 32].

The major complaint of our patients with HCC was abdominal pain, which was seen in more than 50%. Our earlier study has highlighted the importance of symptomatology (weight loss, anorexia and abdominal pain) as markers for HCC [33]. The strong male predominance in our study (the male to female ratio was 9:1) is similar to the global trend [34].

Serum AFP level >400 ng/ml is taken as a conventional diagnostic level for HCC [35]. In this study, AFP was elevated in 71% of patients, but was above the diagnostic range in only 36% of patients. Low serum levels may be either because of smaller tumors or due to better differentiation of masses that do not produce high AFP [36]. The level of AFP did not show any correlation to the number of tumors or to the etiology of HCC.

An important aspect of the present study was that over a period of time and with the screening program available at our center, more treatable cases were picked up in group II patients as compared to group I [12 (24%) in group I vs. 129 (47%) in group II, $p < 0.01$]. Moreover, patients who underwent therapy at any stage had longer survival compared to untreated patients. On subgroup analysis, this was significant in early tumor stages (BCLC A and B).

Only 14 (10.7%) patients in the present series underwent hepatectomy and none underwent liver transplantation. In India, living donor liver transplantation is still at the nascent stage, with services limited to only 2 centers in the country and hence virtually nonexistent. 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. However, cadaveric liver transplant has been available at our center for 6 months. Additionally, since most of our patients were in BCLC stages B and C, this precluded surgical therapies. The overall median survival in our patient group was only 16 months and the untreated patients had a median survival of 7 months. This poor survival is similar to that reported in other studies [37, 38] and is attributed to the presence of advanced disease at the outset.

Local ablative therapies with their minimal invasiveness form a very important curative treatment modality and are best for small unresectable HCC. While most studies have limited local therapies to tumors <3 cm, we offered these treatments to patients with tumors ≤ 5 cm and ≤ 5 in number. In a randomized control trial, although RFA has been shown to be superior to PAI and percutaneous ethanol injection in local recurrence and overall survival, it caused significantly more complications [39]. PAI on the other hand is inexpensive, easy to use and has a better patient tolerance and safety profile, but requires multiple sessions for tumor necrosis. The mean number of sessions in our study for PAI and RFA were 3.8 and 1, respectively. Lin et al. [39] have shown that RFA required significantly fewer sessions as compared to percutaneous ethanol injection and PAI for complete tumor necrosis [37].

Transarterial therapies like chemoembolization (TACE), radionuclide therapy (TART), and chemotherapy (TAC) have been shown to improve the survival of patients with unresectable multifocal HCC with good residual liver function [40, 41]. TART using rhenium (^{188}Re) was used in 7 patients with unresectable HCC with a median survival of 26 months. The median survival for patients who received TACE was 11 months. In one of the largest experiences of TACE, in 8,510 patients with HCC, the median survival was reported to be 34 months and the 1-, 3- and 5-year survival was 82, 47 and 26%, respectively [42].

Combined interventional treatments like TACE and PAI, RFA followed by TACE or TART and vice versa were used in our patients when use of one modality did not effectively control the disease and the disease progressed [43]. Combined therapy has been shown to benefit and prolong survival in patients with advanced tumors [43]. More than a third of our patients had portal vein involvement (40%), in whom chemoembolization was contraindicated. This limited our therapeutic armamentarium and our ability to increase the survival of these patients to a significant extent.

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-fluorouracil, long-acting octreotide, thalidomide and capecitabine in our patients. Combination of thalidomide and capecitabine was used in advanced HCC in 33 patients in our study. Although developed in the 1950s and later withdrawn, thalidomide is an anti-angiogenic drug and this effect is species specific. Given alone, thalidomide has moderate efficacy, has

been shown to be useful in some patients with advanced HCC and it produces durable stability of disease in approximately one third of patients, with a partial response rate not beyond 10% [44, 45]. 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 [46]. Our patients were too poor to afford sorafenib. Even treatment with cheaper chemotherapeutic drugs used in this study was extremely difficult for them to afford.

When BCLC, CLIP and Okuda were put in a Cox's model in a stepwise manner, Okuda staging emerged as an independent predictor of survival in our patients. None of these staging systems are perfect and these models cannot provide a precise prognosis for individual patients. BCLC staging, however, provides a useful and logical guide for therapy according to the prognostic class.

In conclusion, HBV is the most common cause of HCC in India followed by HCV infection. Prevention of these etiologic agents is the only realistic means of reducing the morbidity and mortality of HCC. The survival of these patients can be improved by aggressively treating HCC, complications of cirrhosis and by controlling etiological factors. Serum AFP is not a very sensitive marker for diagnosis or surveillance and there is an urgent need for better markers and imaging to diagnose smaller tumors. Presence of vascular invasion, Okuda staging and treatment were found to be independently associated with survival.

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