ORIGINAL Prof-1470

HEPATOCELLULAR CARCINOMA;
CHARACTERISTICS A RETROSPECTIVE STUDY OF 34 PATIENTS AT JHL, LAHORE

DR. WASIM AMER
Associate Professor Medicine
Allama Iqbal Medical College,
Jinnah Hospital, Lahore

DR. MUHAMMAD ASHRAF MAJROOH
Associate Professor Community Medicine
Allama Iqbal Medical College, Lahore

DR.MUHAMMAD AKRAM
Assistant Professor Oncology
Allama Iqbal Medical College,
Jinnah Hospital, Lahore

Article Citation:
Amer W, Akram M, Majrooh M A. Hepatocellular carcinoma; Characteristics a retrospective study of 34 patients at JHL, Lahore. Professional Med J Sep 2009; 16(3): 364-369

ABSTRACT... **Introduction:** Hepatocellular carcinoma (HCC) is the commonest primary malignant cancer of the liver in the world. Characteristics of our population suffering from HCC are not known, this study aims to present epidemiological, clinical and laboratory characteristics of HCC patients..**Design:** A retrospective study. **Setting:** At Jinnah hospital, Lahore. **Period:** 36 months. **Material & methods** HCC was diagnosed according to the guide lines given by EASL-2000. The data was later analyzed by SPSS13. **Results.** A total of 34 patients were included in the study. Majority patients were male 21(80%) and belonged to urban setting (21). Pain abdomen 21(61.8%) and Ascites 22(64.7%) were the commonest presentations. 15(44%) patients were suffering from HCV and 12 (35.3%) were negative for both HCV & HBV, while 9 out of these were also not alcoholic. Most of the patients had symptoms present for 1-6 (76%) months and majority presented in either stage III or IV (91%), none of the patient presented in stage I. Most the patients 25(73.5%) had tumor size larger than 5 cm at presentation and similarly 20 (59%) had more than one lesions at presentation, stage of tumor was positively associated ($p < 0.02$) with number of tumor lesions. **Conclusion.** HCC does occur in a cirrhotic background but a good number of patients were not cirrhotic and need to be investigated further for other possible dietary risk factors. Pain and abdominal distension in a cirrhotic patient should be addressed to immediately so as to diagnose HCC at an earlier stage.

Key words: HCC, cirrhotic background, pain, abdominal distension

INTRODUCTION

Hepatocellular carcinoma (HCC) is the commonest primary malignant cancer of the liver in the world. Incidence is increasing and HCC has risen to become the 5th commonest malignancy worldwide and the third leading cause of cancer-related death, exceeded only by cancers of the lung and stomach[1]. The estimated incidence of new cases is about 500 000-1 000000 per year, causing 600 000 deaths globally per year[2-6]. Because of its poor prognosis, this number of deaths is almost the same as the number of cases being diagnosed each year (626 000)[7].

Major risk factors for HCC are well known and are dependent on the geographic area. In Europe, the United States, and Japan, the main risk factors are liver cirrhosis in over 90% cases due to hepatitis B and C virus, alcohol, and tobacco; in contrast, in Africa and Asia, incidence of HCC is higher in non cirrhotic liver diseases,

Article received on: 30/01/2009
Accepted for Publication: 28/02/2009
Received after proof reading: 25/06/2009
Correspondence Address:
Dr. Wasim Amer
88/I – B P.C.S.I.R. Housing Society, Phase – I
Canal Bank Road, Lahore 54590
wtzm@hotmail.com

and attributed to factors like, hepatitis B and C virus infection (even without cirrhosis), tobacco use, and aflatoxin exposure[8,9]. Therefore from a global perspective, the two most important risk factors for HCC are Chronic HBV and HCV infection, leading to cirrhosis. In fact, cirrhosis from any cause is a predisposing factor for HCC and could be considered as a premalignant condition. However, about one quarter of HCC cases diagnosed in the United States do not have any known predisposing risk factors[10].

HCC incidence rates are two to three times higher, but in decreasing trend, in developing countries. However, the figures in the developed countries are contrary. Successful hepatitis B virus (HBV) vaccination programs, better food hygiene, increased global hepatitis C virus (HCV) prevalence and population migration are the possible explanations. Given that the burden of chronic liver disease is expected to rise owing to increasing rates of alcoholism, hepatitis B and C prevalence and obesity-related fatty liver disease, it is expected that the incidence of HCC will also increase in the foreseeable future[11].

A comprehensive analysis of patients with this disease is not available for our patients. This study aims to study the epidemiological, clinical and laboratory characteristics of HCC patients.

MATERIAL & METHODS

The study was conducted at Jinnah Hospital Lahore. It was a retrospective study, and 36 month data from January 2005 to December 2007 was analyzed. All the patients fulfilling the diagnostic criteria for HCC, laid down by Barcelona-2000 EASL conference, were included in the study [12]. All the patients were analyzed for clinical, etiological, lab and radiological profile.

A comprehensive Performa was completed for each patient and it included clinical symptoms and signs e.g. pain, abdominal distension, fever, jaundice, weight loss, mass in abdomen, size of lesion and ascites along with the duration of symptoms. Also was recorded the urban or rural background of the patient, risk factors like smoking and alcohol. The lab investigations included serology for viral hepatitis, Ultrasound abdomen for size, number of lesions, ascites, lymph node enlargement, PV thrombosis and liver parenchyma echotexture. CT scan was done to help classify the stage of the disease. Alpha fetoprotein was also measured for each patient. FNAC was done as needed according to EASL-2000 guidelines[12]. Patients with incomplete data were not included in the study, and as such there were only 2 drop outs, bringing the final number of patients to 34, with 27 males and 7 females (mean age 56.4 yrs).

All the data was later analyzed with SPSS 13. The clinical data was presented in frequency and percentage. Cross tabulations were done between various parameters. For both comparisons chi-square was used as test of significance at p-value <0.05.

RESULTS

There were 34 patients in all, with 27 (80%) being male. Mean age was 56.4 years with youngest being 30 years and eldest being 90 years, 70% of patients were in the age group 25-50 years while 30% were above 50 years. Smoking and alcohol consumption were found in only 30% and 8% patients respectively. Most of the patients 21 (61.8%) belonged to urban settings.

Pain abdomen was the commonest symptom present in 21(61.8%) patients, followed by abdominal distension in 17%, fever and weight loss both in 14%, while jaundice was present in only 6%.

Ultra sound examination revealed that ascites was in fact present in 22 (64.7%) patients and portal vein thrombosis was found in 30% patients. Both pain and ascites increased in frequency as the disease progressed. Of the 21 patients having pain 20(95%) were in stage III and IV, similarly of the 22 patients having ascites, 21(94%) belonged to stage II and IV (Table I).

Serology for viral hepatitis showed that HCV was the commonest being present in 15(44%) patients, 6 had HBV while one patient tested for both viruses. Interestingly 12 (35.3%) patient had a negative serology for both viruses, and 9 of these were non smokers as well.

Table-I. Clinical profile		
Clinical Profile	**Frequency**	**%age**
Symptoms (N=34)		
Pain	21	61.8
Distension	6	17.6
Fever	5	14.7
Jaundice	2	5.9
Weight loss	5	14.7
Mass	2	5.9
Ascites	22	64.7
PV thrombosis	10	29.4
Viral status (N=34)		
HBV	6	17.6
HCV	15	44.1
HBV + HCV	1	2.9
None	12	35.3
Duration from onset of symptoms to diagnosis (N=34)		
<1 month	4	11.8
1-6 months	26	76.5
> 6 months	4	11.8
Stage of the disease (N=34)		
Stage I	1	2.9
Stage II	2	5.9
Stage II	13	38.2
Stage IV	18	52.9
Size of the tumor (N=34)		
<5 cm	9	26.5
5-10 cm	16	47.1
>10 cm	9	26.5
Number of lesion (N=34)		
Solitary	14	41.2
Multiple	20	58.8

Male to female ratio was almost similar in both HBV and HCV patients (83% & 86% males respectively).

It was rare for a patient to have symptoms and to have kept waiting for more than 6 months before presenting to hospital (12%). Early presentation, within one month, of onset of symptoms was also not common (12%). Rest of the patients (76%) had duration of symptoms ranging from 1-6 months.

None of the patients belonged to the accidentally diagnosed category. Most of the patients (91%) belonged to stage III 13 (38%) and IV 18 (53%), while no patient was in stage I at the time of presentation. Similarly lesions smaller than 5 cm were found in 9(26.5%) patients while rest (73.5%) had lesions bigger than 5cm, 26.5% had lesion bigger than 10 cm. Patients with tumors larger than 10cm belonged to stage III (33.3%) and IV (66.6%) respectively.

A solitary lesion was found in 14 patients while rest 20(59%) had multiple lesions. None of the patient with multiple lesions belonged to stage II, all 3 patients in this stage had solitary lesion and the size in 2 of these was less than 5cm as well. All the patients with multiple lesions were in stage III 6 (30%) and IV 14 (70%). Out of 18 patients belonging to stage IV, 14(77.8%) had multiple lesions. Stage of tumor was positively associated with number of lesions with a p-value < 0.02. There was no difference in the number of lesions regarding the HBV or HCV status of the patients (Table II).

Alpha feto protein was measured in each patient with values ranging from less than 100 to more than 50 thousand IU. Majority 14 (41%) had a value less than 100 IU and out of these 8(44%) belonged to stage IV. As such no significance was found between AFP levels and the stage, size or number of lesions. Similarly no significance was found between portal vein thrombosis and size, no of lesions or the stage of the disease.

Table-II. Cross tabulation of Stage of disease, Size of Tumor and Tumor lesions						
Stages		Size of Tumor			Tumor Lesions	
		<5 cm	5-10 cm	>10 cm	Solitary	Multiple
Stage I	No	2	1	-	3	-
	%age	22.2%	6.3%		21.4%	
Stage II	No	4	6	3	7	6
	%age	44.4%	37.5%	33.3%	50%	30%
Stage III	No	3	9	6	4	14
	%age	33.3%	56.3%	66.6%	28.6%	70%
Total	No	9	16	9	14	20
	%age	100%	100%	100%	100%	100%

Chi-Square Tests Stage of disease & tumor lesions			
Stage of disease & Tumor Lesions	Value	d f	Asymp Sig (2 sided)
Pearson Chi-Square	7.817	2	.020
Likelihood Ratio	9.055	2	.011
N of valid case	34	-	-

DISCUSSION

It was a small study consisting of 34 patients. Mean age turned to be 56.4 years. The incidence of HCC increases with age, probably a surrogate for the duration of underlying disease, reaching its highest prevalence among those aged over 65 years. Although HCC is rare before the age of 50 years a shift in incidence towards younger persons has been noted in the last two decades[13,14,15]. In this study too majority of patients were less than 50 years in age. The reason for the change in this trend is under discussion. The reason in this study could be the infection of HCV at an earlier stage.

The calculation of the risk associated with any epidemiological or clinical variable is difficult to establish. Most studies on the incidence of HCC are uncontrolled and are clinically based, rather than population based. Thus, relevant predictors in the general population may remain undetected. Male sex is associated with a higher incidence. Same was true in this study with 80% being male. However, the most powerful risk factor is the existence of liver cirrhosis regardless of its etiology[16]. Majority (65%) patients in this study also had Chronic liver disease due to either HBV or HCV infection, and in the rest of the patients there was no obvious cause for cirrhosis, but chronic liver disease was present nonetheless.

Apart from the difference in the carcinogenic mechanisms, there are a number of clinical differences between HBV- and HCV-related HCC. For reasons yet to be known there is a larger proportion of male HBV infected patients with HCC than the HCV counterpart. The male-to-female ratio is higher in HBV-related HCC than in HCV-related HCC (6.7:1 and 3.3:1 respectively in one study)[17]. Studies consistently show that HCC develops 10 years earlier in HBV carriers than in HCV carriers, though we did not find such a difference in this study.

Due to the different mechanisms involved in carcinogenesis in HBV and HCV patients, their rate of HCC development is also different. HBV infection leads to the development of HCC through direct and indirect pathways as it has the ability to integrate into the host genome affecting cellular signaling and growth control. HCV causes HCC mainly through indirect pathways: chronic inflammation, cell deaths and proliferation. As a result, HCC is almost exclusively found in cirrhotic HCV

patients while HCC is sometimes found in HBV patients without significant liver cirrhosis[11]. The cumulative rates of HCC at 5, 10 and 15 years continue to increase with 6.5%, 23.4% and 31.9% for patients with HBV-related cirrhosis, and 4.6%, 24% and 56.2% for patients with HCV-related cirrhosis, respectively[18]. At the time of HCC diagnosis, a higher proportion of HCV infected patients than HBV infected patients has advanced liver histology and has a higher Child Pugh's score[17].

The HCC tumor size and the growth pattern also tend to be different between HBV- and HCV-related HCCs. In most patients with HCV-related HCC, the tumors are more likely to be solitary, smaller sized and encapsulated whereas HBV-related HCC are more commonly infiltrative and multinodular[18]. Extensive hepatic involvement and portal vein invasion by the tumor has been reported in HBsAg-positive HCC patients compared to HBsAg-seronegative HCC patients[19]. Again in this study no such relation was found. Not only was the study size small but majority of patients were HCV positive. Successful vaccination at birth has resulted in a decrease in the overall reporting of chronic HBV patients in our set up.

No significant relationship was found between AFP positivity and tumor size, tumor encapsulation, degree of vascular invasion, or the stage of the tumor. Similar observations have been reported internationally as well. However, patients with AFP-positive carcinomas had a poorer prognosis than those with AFP-negative carcinomas (5-year survival rate of AFP-positive and negative groups were 26.7% and 56.5%, respectively)[20].

CONCLUSION

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer and the most severe complication of chronic liver disease. The characteristics of our patients doesn't differ much from the western patients, but a good number of patients in this study were not cirrhotic and need to be investigated further for other possible dietary risk factors.

Pain and abdominal distension in a cirrhotic patient should be addressed to immediately so as to diagnose HCC at an earlier stage. The stages of the malignancy as well as the severity of the underlying liver disease are essential factors in planning the therapeutic approach. Curative treatment options are limited, represented mainly by surgery (i.e. resection or transplantation), but most patients report late and are already in stage II or IV at presentation. Therefore, majority is as such not candidate for a curative option, and only palliative treatment could be given to these patients.

REFERENCES

1. World Health Organization. **Mortality database.** Available from : URL: http://www.who.int/whosis/en.
2. Parkin DM, Pisani P, Ferlay J. **Estimates of the worldwide incidence of 25 major cancers in 1990.** Int J Cancer1999;80:827-841.
3. Montalto G, Cervello M, Giannitrapani L, Dantona F, Terranova A. **Epidemiiology, risk factors and natural history of hepatocellular carcinoma.** Ann N Y Acad Sci 2002;963:13-20.
4. Sherman M. **Hepatocellular carcinoma: epidemiology, risk factors and screening.** Semin Liver Dis 2005;25:143-44.
5. Parkin DM, Bray F, Ferlay J, Pisani P. **Global cancer statistics,** 2002. CA Cancer J Clin 2005;55:74-108.
6. Yeh CT, Chen TC, Chang ML, Hsu CW, Yeh TS, Lee WC, Huang SF, Tsai CC. **Identification of NV-F virus DNA in hepatocellular carcinoma.** J Med Virol 2007;79:92-96.
7. Ferlay J, Parkin DM, Pisani P. **Globocan graphical package 1: cancer incidence and mortality worldwide.** Lyon:IARC press 1998.
8. Montallo G, Cervello M, Giannitrapani L, Dantona F, Terranova A, Castagnetta LA. **Epidemiology, risk factors, and natural history of hepatocellular carcinoma.** Ann N Y Acad Sci 2002;963:13-20.
9. Okuda K. **Hepatocellular carcinoma.** J Hepatol 2000;225-237.
10. Raoul JL. **Natural history of hepatocellular carcinoma and current treatment options.** Semin Nucl Med. 2008 Mar ;38(2):S13-18.
11. But DY. Lai CL, Yuen MF. **Natural history of hepatitis-related hepatocellular carcinoma.** World J Gastroenterol. 2008 Mar ;14(11):1652-56.
12. Jordi B, Morris S, Jessop ML, Michel B, Riccardo L, Andrew

KB etal. **Clinical management of hepatocellular carcinoma. Conclusions of Barcellona – 2000 EASL conference.** J Hepatol. 2001 September ;35(3):421-430.

13. El-Serag HB. **Epidemiology of Hepatocellular carcinoma in USA.** Hepatol Res 2007;37 supp2: 88-94.

14. Parikh S, Hyman D. **Hepatocellular cancer: a guide for the internist.** Am J Med 2007; 120: 194-202.

15. Bosch FX, Ribes J, Diaz M, Cleries R. **Primary liver cancer: world wide incidence and trends.** Gastroenterology 2004;127:s5-16.

16. Zamman SN, Melia WM, Johnson RD, Portman BC, Johnson PJ, Williams R. **Risk factors in development of hepatocelleular carcinoma in cirrhosis: prospective study of 613 patients.** Lancet. 1985;1:1357-60.

17. Shiratori Y, Shiina S, Imamura M, Kato N, Kanai F. **Characteristic difference of hepatocellular carcinoma between hepatitis B and C viral infection in Japan.** Hepatology 1995; 22:1027-33.

18. GentiliniP, Melani L, Riccardi D, Casini RV, Romanelli RG. **Hepatocellular carcinoma and viral cirrhosis.** Hepatology 1994;20:764-65.

19. Shijo H, Okazaki M, Koganemaru F, Higashi M, Sakaguchi S. **Influence of hepatitis B virus infection and age on mode of growth of hepatocellular carcinoma.** Cancer 1991;67:2626-32.

20. Izumi R, Shimizu k, Kiriyama M, Hashimoto T, Urade M, Mizukami Y. **Alpha-fetoprotein production by hepatocellular carcinoma is prognostic of poor patient survival.** J Surg Oncol 1992;49:151-55.

PREVIOUS RELATED STUDIES

Abdul Rahim Siyal, Sher Mohammad Sheikh, Abrar Shaikh, Siraj Ahmed Abbasi, Akbar Ali Soomro. Pattern of Hepatocellular Carcinoma in Interior Sindh. Professional Med J Sep 1999; 06(3):372-378