
RESEARCH COMMUNICATION

Survival from Hepatocellular Carcinoma at a Cancer Hospital in Pakistan

Muhammed Aasim Yusuf*, Farhana Badar, Fouzia Meerza, Rizwan Anwar Khokhar, Faiqa A Ali, Shahbaz Sarwar, Zia Salman Faruqi

Abstract

Objectives: To determine the tumour and general characteristics, especially survival, of patients presenting with hepatocellular carcinoma at our tertiary care cancer hospital. **Patients and methods:** We retrospectively studied 584 charts of patients consecutively registered between 1995 and 2004 at the Shaukat Khanum Memorial Cancer Hospital and Research Centre, in Lahore, Pakistan. Descriptive statistics were obtained for gender, age, tumour size and morphology, alpha fetoprotein level, means of diagnosis, Child-Pugh status, risk factors, treatment given and follow-up. Survival analysis was conducted using the Kaplan-Meier method. **Results:** Mean age at presentation was 56 years. Four hundred and forty four (76%) were male. Average tumour diameter evaluable in 412 patients was 8 cm. HCC was unifocal in 194 (33%), multifocal in 303 (52%) and unevaluable in 106. Mean AFP was 4,198 u/ml (range 1 - 278,560). Methods of diagnosis were FNA in 71, biopsy in 26, imaging/AFP > 200 in 70, lipiodol angiogram in 42, combinations of two of these in 365 and biphasic CT scans in 10. Initial Child-Pugh available for 400/584 was A in 216, B in 147 and C in 37. Evidence of prior hepatitis B infection was found in 114, and for hepatitis C in 254. Other than the four patients who had TACE followed by surgical resection, treatment was offered to 79/584 patients: among the 48 who had TACE, 26 experienced cancer progression whereas 11 had stable disease ranging from 6 - 20 months; another 11 were lost to follow-up. Of the 14 patients who underwent local resection, 2 were lost to follow-up, 7 developed recurrences but 5 remained disease free for a mean of 33 months. Following ethanol ablation in 17 patients, disease progressed in 5 but remained stable in 2 for a mean of 13 months; 10 were lost to follow-up. At the time of writing, 56 patients are alive (mean follow-up 20 months), 210 are known to have died (mean follow-up 9 months), and 318 were lost to follow-up within 3 months. Median overall survival was 10.5 months, death being the point of interest for survival analysis. Child-Pugh class stratified analysis (400/584) revealed median survival of 12 months for class A, 7.7 months for class B and 4 months for class C ($p < 0.001$). **Conclusions:** Most patients present with large, multifocal tumours, with poor liver function. Sixty one percent had evidence of prior infection with hepatitis B or C. The advanced stage at presentation, poor background liver function in many and the absence of a national liver transplantation program limit treatment options. Only 14% of patients were considered suitable for definitive treatment. Survival correlated with Child-Pugh status at presentation. Overall prognosis remains bleak. There is an urgent need to educate the public about the risks of hepatitis B and C and health professionals about early diagnosis and treatment, including possible development of a sustainable national liver transplant program.

Key Words: Hepatocellular carcinoma - patient characteristics - survival - Pakistan

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Introduction

HCC is the fifth commonest cancer worldwide, with more than one million new cases diagnosed each year (ACS, 2006). Annual incidence in Pakistan is 8/100,000 (Bhurgri, 2004). Hepatitis C and B (Mujeeb et al., 1997; Khokhar et al., 2003; Bukhtiar et al., 2003) have been found to be the leading causes in Pakistan. Patients at an early stage may achieve a 5-year survival rate above 50%, those at intermediate-advanced stage have 20-50% survival at 3 years and those at terminal stage die within six months (Llovet et al., 2002). There is a dearth of data regarding HCC in Pakistan.

Patients and Methods

We set out to analyze data, to obtain descriptive results and survival information, on 584 patients seen with HCC at our tertiary care cancer hospital (the Shaukat Khanum Memorial Cancer Hospital and Research Centre) in Lahore, Pakistan, between 1995 and 2004, using information from the computerized Hospital Cancer Registry as a part of Outcomes Research. Descriptive statistics were obtained on gender, age, tumour size, tumour morphology, alpha fetoprotein level, means of diagnosis, Child-Pugh status, risk factors, treatment given and follow-up. Survival analysis was conducted using the

*Department of Internal Medicine, Shaukat Khanum Memorial Cancer Hospital and Research Centre, 7/A Block R-3, MA Johar Town, PO Box 13014, Postal Code 54770, Lahore, Pakistan. *For Correspondence: Email aasim@skm.org.pk*

Kaplan-Meier method to estimate the survival function at the time of each event. Death being the event of interest, time interval from diagnosis till death was computed. Results were considered significant at an alpha-level of 0.05. The Statistical Package for Social Sciences (SPSS), version 10, was used to generate the results.

Results

Seventy-six percent (444/584) were male; mean age at presentation was 56 years; mean weight at initial presentation was 65 kg in 311 patients with a recorded weight. Tumour cross-sectional diameter was available in 412 patients. The mean was found to be 8 cm. We had data on tumour morphology in 497 patients; HCC was unifocal in 194 patients (33%) and multifocal in 303 (52%). AFP values were available in 442 patients. The mean AFP level was 4,198 u/ml, with a very wide range from 1 to 278,560. The median value was 262, with a mode of 300.

The means of diagnosis in these 584 patients were as follows. FNA in 71, biopsy in 26, combination of appropriate findings on an imaging modality and an alpha fetoprotein (AFP) level of greater than 200 in 70, lipiodol angiography in 42, a combination of at least two of these modalities (appropriate findings on an imaging modality, AFP level of greater than 200, cytology or histology) in 365 and characteristic appearances on a biphasic CT scan alone in 10.

Child-Pugh status at initial presentation was assessed in 400 patients. 216 patients were Child-Pugh class A, 147 class B and 37 class C.

Risk factors for HCC included evidence of hepatitis B infection in 114, evidence of hepatitis C infection in 254, diabetes mellitus in 123 and tattooing in 1. Treatment was offered to only 79/584 patients. This was due to a number of factors, including the large mean tumour size at presentation, the multifocal nature of disease in the majority and the presence of an advanced stage of liver disease in just under half the patients.

Forty eight patients underwent transarterial chemoembolization (TACE) using lipiodol and doxorubicin. Of these, there was evidence of disease progression in 26, 11 had stable disease for a minimum of six months (range 6 - 20 months) and 11 were lost to follow-up.

Fourteen patients underwent local resection. Of these, 5 have been disease free for a mean period of 33 months, 7 developed recurrent disease and 2 were lost to follow-up shortly after surgery.

Table 1. Survival Analyzed by Child-Pugh Status using the Kaplan-Meier Method

Child-Pugh status	Total	Deaths recorded	Mean survival*	Median survival*	95% CI
A	216	88	31.7	12.0	7.48, 16.58
B	147	66	13.7	7.7	4.41, 10.99
C	37	12	13.3	4.1	2.52, 5.74
Total	400	166	24.0	10.5	8.40, 12.66

* months

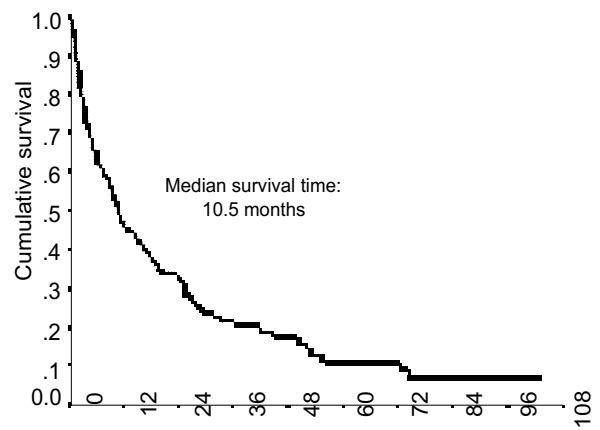


Figure 1. Overall Survival of Patients with HCC

Percutaneous ethanol injection (PEI) was performed in 17 patients. Of these, 5 progressed within three months of treatment, 2 had stable disease for a mean of 13 months and 10 were lost to follow-up. Four patients underwent TACE followed by surgical resection.

The follow-up period was computed as the time interval between the date of diagnosis and date of death/last visit. At the time of writing, 56 patients are alive (mean follow-up 20 months), 210 are known to have died (mean follow-up 9 months), and 318 patients were lost to follow-up within 3 months.

Survival Analysis

Using the Kaplan-Meier procedure, the overall survival of the patients was determined, death being the point of interest. Median overall survival was 10.5 months (95% CI 8.46, 12.74) (Figure 1).

The 1-year cumulative probability of survival was 45%, 3-year was 20% and 5-year was 10%. Analyzing survival by Child-Pugh class at presentation provided additional information as shown in Table 1.

Log Rank Statistic testing for equality of survival distributions was significant (log-rank statistic = 16.14, df = 2, p < 0.001). The difference in median survival between patients in Child-Pugh class A and B was statistically significant (p < 0.001). The difference in survival between Child-Pugh class A and C was also statistically significant (p = 0.01). The difference in survival between Child-Pugh class B and C was not significant however (p > 0.05). The survival distributions by Child-Pugh class are shown in Figure 2.

Discussion

Hepatocellular carcinoma is a commonly occurring tumour in Pakistan. Data from the Karachi tumour registry, the only population-based tumour registry in Pakistan, have shown a population prevalence of 8/100,000 (Bhurgri, 2004). At our tertiary care cancer hospital, HCC is the eighth commonest tumour we see. The majority of our patients appear to present with advanced disease, with large, (mean cross-sectional diameter 8 cm.) multifocal disease. Background liver function, as assessed by the Child-Pugh status, was poor (B to C) in 46%. Prior infection with hepatitis B or C is the single biggest risk-

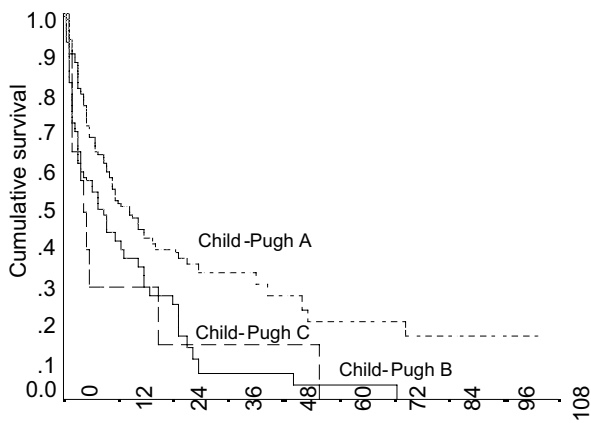


Figure 2. Graph Depicting Difference in Survival by Child-Pugh Class

factor, with a full 61% of all HCC patients seen having evidence of prior infection with hepatitis B or C.

All patients seen with hepatocellular carcinoma at our institution are discussed at a multi-disciplinary meeting attended by hepatologists, radiologists, pathologists and surgeons with an interest in hepatic surgery. The advanced stage at presentation, as well as poor background liver function in many, coupled with the absence of a liver transplantation programme in Pakistan (Abbas et al., 2002), means that treatment options are few. Only 14% of patients were considered suitable for anything other than supportive/symptomatic care. The commonest procedure performed was TACE, with smaller numbers undergoing PEI and surgical resection of tumours. Since completion of this study, we have also introduced RFA at our institution.

The median survival following diagnosis was 10.5 months. The 1-year survival was 45%, 3-year survival 20% and 5-year survival 10%. There are few comparative survival data published from Pakistan. One series of patients treated with TACE reported a median survival of 13.6 months in a group of 35 patients treated with TACE (Haider et al., 2006). We found that survival correlated strongly with Child-Pugh status at presentation. Thus mean survival for Child-Pugh class A patients was significantly longer than that for Child-Pugh class B. The difference in survival between patients in Child-Pugh classes A and B ($p < 0.001$) and between classes A and C was also statistically significant ($p = 0.01$). The difference in survival between Child-Pugh class B and C was not significant however ($p > 0.05$). This difference in survival between Child-Pugh classes was also seen in an earlier study from Pakistan which examined survival following TACE (Haider et al., 2006).

In our experience, most patients with hepatocellular carcinoma present with large, multifocal tumours, with poor background liver function and evidence of prior infection with hepatitis B or C in the majority. The advanced stage at presentation, poor background liver function and the absence of a national liver transplantation program limit treatment options. Only 14% of our patients were considered suitable for definitive treatment. Survival correlated with Child-Pugh status at presentation. The overall prognosis remains bleak. There is an urgent need

to educate the public about the risks of hepatitis B and C, and health professionals about early diagnosis and treatment for HCC. Urgent consideration needs to be given to the development of a sustainable national liver transplant programme in our country.

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