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A simple prognostic scoring system for patients with unresectable hepatocellular carcinoma treated by chemo-embolization

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Abstract

Background: Hepatacellular carcinoma (HCC) comprises heterogeneous groups of patients with differing outcomes. *Methods*: In order to attempt to identify patient sub-sets, we retrospectively examined the records of 750 patients with biopsy-proven unresectable HCC, who were treated with hepatic artery chemo-embolization and were followed till death. We used the Cox proportional hazard model, as it was neutral with respect to prejudged cut-off between short and long survival. *Results*: On univariate analysis, we found a shorter survival to be associated with male gender, presence of cirrhosis, portal hypertension, portal vein thrombosis and elevations of bilirubin, GGTP, ALKP, AFP, DCP, PT and albumin. Five factors were found to be statistically significant ($p < 0.05$) on multivariate analysis, namely presence of cirrhosis or ascites and elevations of AFP, ALKP or GGTP. We developed a simplified scoring system based upon the sum of the hazard ratios of each of these five factors. By combining the two factors with the heaviest hazard ratios from our multivariable analysis, namely AFP (+ = >100 ng/mL) and ALKP (+ = >100 IU/mL), we found a simple parsimonious prognostic tool, which segregated the patients into survival groups, namely AFP− ALKP−; either AFP+ or ALKP+; and AFP+ ALKP+; these three groups corresponded to a 24-month survival of 70%, 32% and 12%, respectively. *Conclusion*: we found that only two lab functions, AFP and ALKP levels, in our large HCC patient cohort undergoing hepatic artery chemo-embolization, had prognostic significance.

Keywords: Unresectable; Hepatocellular Carcinoma; Prognostics; Hazard ratio; Survival; Kruskal-Wallis one-way analysis variance; Kaplan-Meier test; Breslow test; Multivariate analysis; Esophageal varices; Tumor vascularity; Portal vein thrombus; Hepatitis B; Hepatitis C

1. Introduction

Hepatocellular carcinoma (HCC) comprises a variety of sub-sets of patients, often with quite different prognosis. This is reflected in different survival data published for either resection or chemo-embolization (TACE) from various centers as well as the wide range of survivals using the same treatment modality even within any individual large center. In recent years, several attempts have been made to introduce a prognostic scoring system, in order to identify those patients with potentially better or worse outcomes after receiving treatment. These have been useful, particularly for consideration of resection, or liver transplant. The earliest widely used prognostic scoring system was that of Okuda et al. [1], which was in general use for many years. This was subsequently refined with the introduction of the CLIP [2,3] scoring system for patients with cirrhosis, from Italy that has found general use. Recently additional systems have been introduced, including a BCLC system from Barcelona [4,5], a Hong Kong [6] and a Tokyo [7] scoring system and several others [8]. Each system has its advocates [9,10], and it is not yet clear which is the most widely applicable combined with the simplest use. None of these systems have really been applied to identifying patients with unresectable tumors

Abbreviations: HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; DCP, des gamma carboxy prothrombin; ALKP, alkaline phosphatase; GGTP, gammaglutamyl transpeptidase; PT, prothrombin time; PVT, portal vein thrombosis; WBC, white blood count; SGPT, serum glutamine pyruvic transaminase; CAT, computerized axial tomography; HR, hazard ratio

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who only receive medical treatment and are usually assigned to the, palliative care, sub-set of patients for whom prolonged survival as a result of treatment is not considered likely. However, within this very large proportion of unresectable HCC patients, there are also several sub-sets. In order to try to identify possible groupings of patients who might have better prognosis within this large and heterogeneous group of HCC patients, we have examined the radiological and laboratory parameters of a very large cohort of patients treated by one individual in a single institution and followed prospectively over multiple years. The data in this report comprise an attempt to evaluate this large set of patients who were treated only with chemo-embolization using cisplatin, in order to identify possible prognostic sub-sets that might be put to formal testing in the future.

2. Materials and methods

All patients in this retrospective study had biopsy-proven HCC and were considered to be surgically unresectable. They underwent cisplatin-based hepatic arterial chemotherapy between 1989 and 1999 at the Liver Cancer Center of the University of Pittsburgh Medical Center. The clinical, pathological and laboratory data were collected and entered into the Liver Cancer Center registry and database, with the approval of the University of Pittsburgh IRB. The lab data included complete blood count, liver function tests, HCC tumor markers and hepatitis serology. The baseline CAT scans were evaluated and assessments were made of the presence or absence of cirrhosis or portal hypertension, number of tumors, maximum tumor size and presence or absence of tumor vascularity or portal vein thrombosis in the main or main branch portal vein. Date of first treatment and date of death were recorded and used for determination of survival.

2.1. Statistical analysis

Continuous variables are reported as mean and standard deviation of the mean. Categorical variables are reported as frequencies. For comparison of lab data between various patient subgroups, the Kruskal–Wallis one-way analysis variance by ranks test was used. For comparison of CAT scan characteristics, chi-square test or Fisher's exact test were used, when appropriate. Patient survival was estimated with the Kaplan–Meier method and comparison of survival was made with the Breslow (generalized Wilcoxon) test. The Breslow test was used, as opposed to the log rank test, due to the large proportion of patients who died early after beginning of treatment, since the study aim was to attempt to identify these early losses. For multivariable analysis, the stepwise proportional hazard Cox regression model was employed. p values <0.05 were considered to be statistically significant.

3. Results

Ninety-five percent of the patients with hepatocellular carcinoma (HCC) that were referred to the Liver Cancer Center (LCC) of the University of Pittsburgh Medical Center, were found to be unresectable and untransplantable, likely due to absence of guidelines in the US for surveillance of patients at risk. These 750 patients, who could only be treated medically, are the subject matter of the current report. We have retrospectively analyzed this large clinical cohort of HCC patients. Their clinical characteristics and outcomes were organized in the form of a database, which was analyzed for the present study. Our primary goal was to examine patient survival and the factors that might affect it. We initially performed a univariate analysis on all 750 patients. We examined laboratory characteristics, liver disease characteristics and tumor characteristics from the CAT scans. Of the 750 patients, 562 (76%) had cirrhosis, 222 (27.9%) had portal hypertension, 252 (31.7%) had ascites, 228 (28.6%) had portal varices, and 282 patients (35.4%) had macroscopic portal vein thrombosis on their CAT scan (Table 1A). Regarding the number of tumors in the liver, 218 patients (27.4%) had one tumor, 193 patients (24.2%) had two tumors and 349 patients (43.8%) had three or more tumors. With respect to their etiology, 456 patients (57.3%) had no alcohol history, and 200 patients (25.1%) had a significant alcohol history that included five or more drinks a day for a period of 20 years or more. The remainder had an intermediate history. 25.6% of our patients were found to be HCV antibody positive, and 15.3% were HBV positive as judged by hepatitis B surface antigen and hepatitis B core antibody positivity. The lab values are also presented in Table 1B, as means $\pm$ standard deviation, and range of values for each parameter (min. and max.). Those factors that were found to be significant, using the Breslow test, are shown with their significance values in Table 1C. We found the significant factors to be presence of cirrhosis, portal hypertension, ascites, portal vein thrombosis, DCP and AFP levels, prothrombin time, alkaline phosphatase, GGTP, total bilirubin value and gender. The proportional Cox regression model found that cirrhosis, ascites, ALKP, AFP and GGTP are five independent predictors of patient survival (Table 2). A hazard score equal to the sum of the hazard ratios corresponding to each of these five factors was obtained for every patient (Table 2). Patients were then grouped into two cohorts: (1) patients with a total hazard score <3 and (2) patients with a total hazard score ≥ 3. Whereas the median survival of the first cohort of patients was 23 months, the median survival of the second cohort of patients was 8 months. Patients' 12 months survival was 69.1% and 40.2%, respectively, for these two cohorts (Fig. 1A). Thus, in Table 2, if any combination of two or more hazard ratios (HR) for any individual patient, gave a combined score of less than 3, then that patient would be represented in the better survival curve (upper line) of Fig. 1A. Otherwise, the patient would be in the lower line of Fig. 1A, representing a