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Development of Hong Kong Liver Cancer Staging System With Treatment Stratification for Patients With Hepatocellular Carcinoma

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BACKGROUND & AIMS: We aimed to develop a prognostic classification scheme with treatment guidance for Asian patients with hepatocellular carcinoma (HCC). **METHODS:** We collected data from 3856 patients with HCC predominantly related to hepatitis B treated at Queen Mary Hospital in Hong Kong from January 1995 through December 2008. Data on patient performance status, Child–Pugh grade, tumor status (size, number of nodules, and presence of intrahepatic vascular invasion), and presence of extrahepatic vascular invasion or metastasis were included, and randomly separated into training and test sets for analysis. Cox regression and classification and regression tree analyses were used to account for the relative effects of factors in predicting overall survival times and to classify disparate treatment decision rules, respectively; the staging system and treatment recommendation then were constructed by integration of clinical judgments. The Hong Kong Liver Cancer (HKLC) classification was compared with the Barcelona Clinic Liver Cancer (BCLC) classification in terms of discriminatory ability and effectiveness of treatment recommendation. **RESULTS:** The HKLC system had significantly better ability than the BCLC system to distinguish between patients with specific overall survival times (area under the receiver operating characteristic curve values, approximately 0.84 vs 0.80; concordance index, 0.74 vs 0.70). More importantly, HKLC identified subsets of BCLC intermediate- and advanced-stage patients for more aggressive treatments than what were recommended by the BCLC system, which improved survival outcomes. Of BCLC-B patients classified as HKLC-II in our system, the survival benefit of radical therapies, compared with transarterial chemoembolization, was substantial (5-year survival probability, 52.1% vs 18.7%; $P < .0001$). In BCLC-C patients classified as HKLC-II, the survival benefit of radical therapies compared with systemic therapy was even more pronounced (5-year survival probability, 48.6% vs 0.0%; $P < .0001$). **CONCLUSIONS:** We collected data from patients with HCC in Hong Kong to create a system to identify patients who are suitable for more aggressive treatment than the currently used BCLC system. The HKLC system should be validated in non-Asian patient populations and in patients with different etiologies of HCC.

Keywords: TACE; Overall Survival; Outcome; Prediction Model.

Hepatocellular carcinoma (HCC) is the sixth leading type of cancer worldwide, with most of the disease burden in Asia and Africa.[1] It carries poor overall prognosis, making it the third most common cause of cancer-related death worldwide.[1]

The natural history of HCC may vary according to its underlying causes. Geographic differences in HCC incidence largely reflect the differences in etiologies. In Western countries, hepatitis C virus (HCV) infection is the main attributable factor, as well as alcohol-related cirrhosis and possibly nonalcoholic fatty liver disease.[2–5] In contrast, in most Asian countries and Africa, the high incidence of HCC is associated with endemic hepatitis B virus (HBV) infection.[3,4]

Staging of HCC differs significantly from other tumor types because the underlying liver disease may have a significant impact on prognosis apart from the biology of the tumor per se.[6] There are a number of integrated staging systems for HCC developed in different parts of the world that take into account both tumor progression and liver function,[7–12] yet none of them universally is adopted or preferred. Of note, the Barcelona Clinic Liver Cancer (BCLC) staging classification[10,13–16] is widely adopted because it is the only staging system that links prognostic classification to treatment indications. The BCLC therapeutic flow-chart has been endorsed by both the European Association for the Study of the Liver[17] and the American Association for the Study of Liver Diseases.[18] To date, the BCLC staging and treatment algorithm of HCC is the most popular treatment algorithm in Western countries, but not in Asia.[19]

BCLC staging classification was developed mainly based on prognostic analysis of several small cohorts of predominantly HCV-infected patients with early HCC treated by resection, transplantation, or percutaneous ethanol injection, and a cohort of 102 patients with untreated intermediate or

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Abbreviations used in this paper: BCLC, Barcelona Clinic Liver Cancer; CART, classification and regression tree; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HKLC, Hong Kong Liver Cancer; LT, liver transplantation; OS, overall survival; PS, performance status; TACE, transarterial chemoembolization.

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advanced HCC.[10] The staging may not be reflective of cancer progression or prognosis in HCC patients for whom HBV infection is the predominant etiologic factor. Most patients with HCV-associated HCC have significant cirrhosis with impaired liver function, whereas patients with HBV-associated HCC in general have better preserved liver function. Moreover, it is well recognized that a more aggressive treatment approach,[19,20] especially surgical resection, has been adopted in most Asian centers owing to higher case volume and expertise.[19,20] Thus, the BCLC treatment algorithm is not used routinely in the management of HCC patients in Asia. Instead, various consensus guidelines with more aggressive management recommendation for HCC have been established by different countries or organizations in Asia.[21–23] However, these guidelines are based largely on expert opinions without supporting data and thus an appropriate prognostic staging system for HCC with treatment guidelines applicable to Asian patients is needed urgently.

In this study, we developed a new prognostic staging system with treatment guidelines based on a large HCC cohort from a single tertiary referral center in Hong Kong and compared our staging with the BCLC staging classification.

Patients and Methods

Between January 1995 and December 2008, there were 3927 patients diagnosed with HCC who were seen at Queen Mary Hospital in Hong Kong. Nine pediatric patients and 63 patients who died or were censored within 7 days after the first consultation and received no treatment were excluded from the present study. Data for each patient were collected prospectively and entered in a master database. The master database contains 2026 variables, covering demographic, clinical, laboratory, treatment, and survival data of each patient. The relevant data were retrieved from the database for this study, with ethical approval from the local institutional review board.

The diagnosis of HCC was confirmed either by histology or cytology, increased α-fetoprotein level ($\geq$400 ng/mL), or by typical radiologic appearance. In our center, patients were staged mostly by contrast computed tomography scan. All patients with adequate liver function and radiologically resectable tumor were evaluated initially for partial hepatectomy. Patients would be considered for liver transplantation (LT) if they were within the Milan[24] or expanded University of California at San Francisco criteria.[25] If the patients were not surgical candidates, transarterial chemoembolization (TACE) or local ablative procedures such as percutaneous ethanol injection and radiofrequency ablation were offered, depending on tumor size, number, and position. Patients with advanced disease were offered systemic therapy. All the patients were followed up with regular clinical examination, blood tests, and computed tomography scanning until death or last follow-up evaluation in the same hospital.

Statistical Analysis

All eligible patients were allocated randomly into a training set or a test set in an approximately 1:1 ratio. The prognostic staging system and treatment guidelines were constructed using the training set and subsequently were tested in the test set. The overall survival (OS) time was defined as the time from the date of first diagnosis of HCC to the earliest of death, last follow-up evaluation, or the date of data censoring (March 31, 2010). All analyses were conducted using R version 2.10.1,[26] and all *P* values resulted from the use of 2-sided statistical tests without adjustment for multiple testing.

To check the similarity between the training and the test sets, the demographic, clinical, and laboratory characteristics of patients at presentation in the 2 sets were compared using the Pearson chi-square test for categoric variables, the Wilcoxon rank sum test for continuous variables, and the log-rank test for time-to-event data.

The missing data on prognostic factors were filled in by multiple imputation using a stochastic switching regression approach with 5 repeated imputations.[27] Imputation was performed separately on the training set and the test set, with the predictor variables chosen using the same strategy.[27] Each of the imputed sets then was analyzed as if it were complete and the results were pooled by the method presented by Rubin[28] to create inferences that validly reflect sampling variability as a result of imputation. For reporting convenience, on occasions when simple pooling was not applicable (ie, Kaplan–Meier plots and cross-tabulation of staging systems), the results produced using the data of the third imputed set would be displayed. Nonetheless, the results produced by using the other imputed sets were similar.

Development of the Prognostic Classification Scheme

The prognostic classification scheme was constructed using the training set by both statistical methodology and clinical judgment. Four established prognostic factors that have determinative roles in the treatment of HCC, namely Eastern Cooperative Oncology Group performance status (ECOG PS), Child–Pugh grade, liver tumor status, and presence of extrahepatic vascular invasion/metastasis, were selected in building the scheme. Liver tumor status was a composite factor of the size of the largest tumor in the liver, number of tumor nodules, and the presence or absence of intrahepatic vascular invasion (Supplementary Table 1). Intrahepatic vascular invasion includes intrahepatic portal vein branch invasion, left or right portal vein invasion, and main hepatic vein invasion; extrahepatic vascular invasion includes main portal vein invasion and inferior vena cava invasion. All factors were categorized.

There were 2 parts in the scheme: prognostic staging and treatment guidance; the outcomes of interest of these 2 parts were OS and treatment modalities, respectively. Therefore, 2 different methods catering to these 2 different end points were used. In broad strokes, the development flow was as follows: (1) modeling OS based on the 4 prognostic factors using Cox proportional hazards regression[29] to account for their relative effects; (2) constructing a prognostic staging system using clinical judgment with reference to the results of the model; (3) classifying disparate treatment decision rules based on the same prognostic factors using classification and regression tree (CART)[30]; and (4) integrating and reconciling the stages and treatment classes with clinical judgment.

Cox regression models were fitted to the imputed data sets to account for the effects of the prognostic factors on the hazard functions. The proportionality assumption was assessed on each imputed data set by a test based on scaled Schoenfeld residuals.[31] When proportionality was rejected, the time-dependent coefficients were plotted over time and examined,