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A model prediction of long-term prognosis in patients with centrally located hepatocellular carcinoma undergoing hepatectomy

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ABSTRACT

Background and Objectives: The prognostic prediction for centrally located hepatocellular carcinoma (CL-HCC) after hepatectomy has not been well established. We aimed to develop prognostic nomograms for patients undergoing hepatectomy for CL-HCC.

Methods: A cohort of 380 patients who underwent curative hepatectomy for CL-HCC at our hospital between 2009 and 2015 were retrospectively studied. We randomly divided the subjects into training (n = 210) and validation (n = 170) groups. Univariate and multivariate survival analysis were used to identify prognostic factors. Visually orientated nomograms were constructed using Cox proportional hazards models. The performance of the nomogram was evaluated by the area under the ROC curve (AUC), calibration curve and compared with the conventional staging systems.

Results: The statistical nomogram for OS built on the basis of ALBI grade, tumor number, tumor size, classification, hepatectomy methods, capsule formation and microvascular invasion (MVI) had good calibration and discriminatory abilities, with AUC of 0.746 (65-month survival). The nomogram for DFS was based on tumor number, tumor size, classification, HBV-DNA load, capsule formation and MVI, with AUC of 0.733 (65-month survival). These nomograms showed satisfactory performance in the validation cohort (AUC, 0.733 for 65-month OS; and 0.702 for 65-month DFS). The AUC of our nomograms were greater than those of conventional staging systems in the validation cohort.

Conclusion: The established nomograms might be useful for estimating survival for patients with CL-HCC after liver resection.

Introduction

For patients with centrally located hepatocellular carcinoma (CL-HCC), liver resection is still the most commonly used technique to achieve radical tumor eradication [1,2]. Both mesohepatectomy (MH) and extended hepatectomy (EH) can be performed for patients with CL-HCC [3,4]. EH is the usual treatment for patients without cirrhosis, while MH (which requires the removal of Couinaud segments IV, V, VIII ± I) can be utilized in patients with impaired functional liver reserve [5,6]. However, different surgical methods (EH or MH) may affect the postoperative prognosis for patients with CL-HCC [7,8]. Except for surgical methods, other factors including tumor morphology, liver function, performance status, the presence of vascular invasion and some molecular determinants (such as alpha fetoprotein) can also influence long-term prognosis of with CL-HCC [9–13].

Owing to a high incidence of tumor recurrence, overall survival outcomes for patients with CL-HCC after hepatectomy is unsatisfactory [14,15]. To our knowledge, few previous studies have reported risk factors related to long-term survival for patients with CL-HCC after MH or EH. Some prognostic factors of CL-HCC after partial hepatectomy may be different from HCC located in the periphery of the liver. To obtain more accurate prognostic perditions, in the present study, for the first time, we established a prognostic model for patients with CL-HCC following an initial liver resection.

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Patients and methods

The data of patients who underwent hepatectomy for pathologically proven CL-HCCs at the Hepatobiliary center in our hospital between January 2009 and January 2015 were collected prospectively and analyzed retrospectively. Patients were excluded when meeting the following criterion: i) recurrent tumor; ii) indocyanine green retention rate at 15 min (ICG-R15) $\geq$ 15% or Child-Pugh grade C; iii) anticipated liver remnant after hepatectomy more than 50% of functional liver volume (nontumorous liver volume); iv) evidence of extrahepatic metastasis; v) history of other malignancy; vi) patients undergoing R1 resection; vii) patients who had gone other treatments (such as transarterial chemoembolization and radiofrequency ablation) viii) incomplete clinicopathologic data. A cohort of 380 patients were analyzed in the present study. The patients were randomly divided into training (n = 210) and validation (n = 170) groups. The computerized random assignment was performed blindly by a programmer (PG) using a random assignment sequence. The HCC diagnosis was confirmed by histopathology. This study was approved by the Ethical Committee of our hospital.

Classification for CL-HCCs

Qiu et al. has established a classification for CL-HCC in 2013 [8] and the classification was validated in another study [13]. This classification divided CL-HCC patients into four groups based on tumor location and the relationship between tumor and vascular structures. We simplified this classification and the primary type I and II were merged due to the similar prognosis in the two groups, thus only three types were shown in the present study. Type I was defined as tumor arising from the junction between segments IVa and IVb, or between segments VIII and V. In this type, tumors did not invade major vascular structures in the first and second portal hepatis. Type II was defined as tumors arising from segments IVa and VIII (adjacent to the second portal structures), or segments V and IVb (adjacent to the first portal structures). Type III was defined as tumors which occupied a large proportion of the parenchyma between the first and second portal hepatis. In type III, tumors were adjacent to vascular structures in both portal hepatis.

Preoperative liver function evaluation

Albumin-Bilirubin (ALBI) grade were shown to provide a more detailed assessment of the liver function and prognosis of HCC patients [16–18], thus the ALBI grade was utilized to assess liver function for patients with CL-HCC. Patients were divided into grade 1 to 3 by the cut points of linear predictor. The cut points were as follows: ≤ -2.60 (ALBI grade 1), -2.60 to -1.39 (ALBI grade 2), and > -1.39 (ALBI grade 3) [16].

Patient management and procedures

The laboratory tests included hepatitis B and C immunological indexes, DNA level of hepatitis B virus (HBV), serum alpha fetoprotein (AFP) level and liver function. The imaging examinations included abdominal ultrasound, contrast-enhanced computed tomography (CT) scan and/or magnetic resonance imaging (MRI). Hepatectomy was considered when all tumors on preoperative imaging examinations could technically be resected within the liver functional reserve. Liver parenchyma transection was carried out with the Kelly crush technique. The Pringle maneuver was utilized during the procedure if needed.

Follow-up

The median follow-up period was 36.0 months for the training group and 44.0 months for the validation group. Patients were followed up at a 2-month interval in the first one year after surgery and at a 3-month interval thereafter. A contrast-enhanced MRI or CT was carried out once every 6 months or earlier if recurrence was suspected. The time of overall survival (OS) was calculated from the date of hepatectomy to the last follow-up or until death. The time of disease-free survival (DFS) was calculated from the date of liver resection to the date of recurrence (which was confirmed by imaging examinations such as CT and MRI).

Statistical analysis

We randomly allocated patients into training and validation sets. Categorical variables are expressed as number (%) and tested by Chi-square test or Fisher exact test. Continuous variables are presented as mean $\pm$ SD and tested by T-test or Whitney *U* test for variables with an abnormal distribution. The OS and DFS curves were determined using the Kaplan–Meier method and compared using the Log-rank test.

Two nomograms were built up on the basis of the results of the multivariate Cox proportional hazards regression models (using a forward stepwise selection method). Variables to be entered into the multivariate regression analysis were chosen according to the results of univariate analyses ($p < 0.2$). Based on the predictive model with the identified prognostic variables, the nomograms were constructed for predicting 1-, 3-, and 5-year OS and DFS after surgery. The discrimination capabilities of the nomograms were evaluated by the receiver operating characteristic curve and the area under the receiver operating characteristic curve (AUC). The calibration capabilities of the nomograms were assessed by calibration chart. P value less than 0.05 was deemed statistically significant. Statistical analyses was performed by R (http://www.R-project.org).

Results

Tumor recurrence and overall survival

As shown in Table 1, there were no significant differences in baseline characteristics between the training cohort (n = 210) and validation cohort (n = 170) except for ALBI grade. In the training cohort, the 1-, 3-, and 5-year OS rates and DFS rates were 90.9%, 60.2%, and 35.5%; 75.1%, 33.3%, and 18.3%, respectively. The median OS and DFS time were 41.0 and 26.0 months, respectively. In the validation cohort, the 1-, 3-, and 5-year OS rates and DFS rates were 88.2%, 55.2%, and 33.6%; 79.4%, 31.7%, and 20.1%, respectively. The median OS and DFS time in validation cohort were 39.0 and 27.0 months, respectively.

Predictors of OS according to pre- or postoperative data of the training cohort

Univariate predictors of OS are shown in Table 2. In univariate analysis, adverse prognostic factors for OS included: ALBI grade 3, tumor number $\geq$3, tumor size, type II or III in the classification, extended hepatectomy, absence of tumor capsule, presence of MVI.

P values of variables less than 0.2 in univariate analysis were entered into multivariate analysis. The results showed that ALBI grade 3, tumor number $\geq$3, tumor size, type II or III in the classification, extended hepatectomy, absence of tumor capsule, presence of MVI were independent unfavorable prognostic factors for OS (Table 3).

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