Preoperative serum liver enzyme markers for predicting early recurrence after curative resection of hepatocellular carcinoma

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BACKGROUND: Early recurrence of hepatocellular carcinoma (HCC) is associated with worse prognosis after liver resection. This study aimed to investigate the prognostic value of common liver enzyme markers in HCC early recurrence after curative hepatectomy and to establish a simple predictive model for HCC early recurrence.

METHODS: A total of 200 patients who had undergone curative resection for HCC were retrospectively analyzed. The patients were divided into early recurrence (within 2 years) and non-early recurrence groups. Demographical characteristics, preoperative liver function parameters, surgical factors and tumor related factors of the patients were assessed by univariate analysis to identify potential significant predictors for early recurrence after resection of HCC. Parameters with statistical significance were entered into a Cox proportional hazard model to find independent risk factors. Receiver operating characteristic analysis was done to determine optimal cut-off values and the number of combined factors in multi-factor predictive model.

RESULTS: Of 13 potential risk factors for early recurrence identified by univariate analysis, high lactate dehydrogenase (LDH>206 U/L, HR=1.711, *P*=0.006), high aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio (AST/ALT>0.96, HR=1.769, *P*=0.006), elevated alpha-fetoprotein (AFP>8.6 ng/mL, HR=2.079, *P*=0.007), small resection margin (≤1 cm, HR=2.354, *P*<0.001) and advanced TNM stage (TNM III-IV, HR=2.164, *P*<0.001) were independent risk factors for early recurrence of HCC shown by multivariate analysis. Patients with three or more concurrent independent risk factors had significantly higher risk for early recurrence than those with low risk factors. The sensitivity and specificity of this predictive model are 53.6% and 80.7%, respectively (area under curve=0.741, 95% CI 0.674-0.800, *P*<0.0001).

CONCLUSIONS: Preoperative common liver enzyme markers, LDH and AST/ALT ratio, were independently associated with early recurrence of HCC. The combination of serum liver enzyme markers with AFP, resection margin and TNM stage better predicted early recurrence of HCC after curative resection in a simple multi-factor model.

(*Hepatobiliary Pancreat Dis Int 2015;14:178-185*)

KEY WORDS: hepatocellular carcinoma; liver enzyme; recurrence; resection; hepatectomy

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers with an increasing incidence worldwide.[1] In recent decades, hepatectomy has become a safe and effective procedure for HCC with a low perioperative mortality.[2] Although hepatectomy remains a most frequently used curative therapy for HCC, long-term prognosis after liver resection remains unsatisfactory because of a high incidence of recurrence.[3, 4] Tumor recurrence after hepatectomy may originate from either intrahepatic metastasis of primary HCC or *de novo* carcinogenesis from the remnant liver, which could be discriminated by different time of recurrence and different risk factors. The prognosis of patients who suffer from early recurrence is extremely dismal.[4] Therefore, early recurrence is considered as an important adverse prog-

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doi: 10.1016/S1499-3872(15)60353-8
Published online March 18, 2015.

nostic factor after curative therapy for HCC.[5, 6]

Since early recurrence is associated with worse clinical outcome, identifying patients at high risk for early recurrence may help improving the prognosis of this population by active surveillance, prevention and treatment of recurrent disease. Although studies[4, 7] suggested tumor pathologic factors and types of surgery[8, 9] as risk factors for early recurrence of HCC, the use of these parameters is of technical difficulties and could not dynamically predict recurrence risk in daily medical practice. In this study, we investigated whether widely-available liver enzyme tests in combination with other readily-available clinical parameters could predict early recurrence of HCC.

Methods

Patients

The patients who had undergone curative resection for HCC at the Department of Hepatobiliary Surgery, the Affiliated Drum Tower Hospital of Nanjing University Medical School between May 2007 and May 2011 were retrieved from a prospectively maintained database and were analyzed retrospectively. Only patients with complete follow-up data and required clinical information were included. The data of the patients were collected and cross-checked by two authors (WZX and JCP) and reviewed by a senior author (DYT) for determination of inclusion. Reasons for exclusion included previous surgical interventions for primary HCC at other institutions, loss of required data, unavailable follow-up data, perioperative mortality and non-curative resections, etc. Finally, 200 patients were enrolled in this analysis. Curative resection was defined as complete excision of HCC without identifiable gross or microscopic tumor and no residual tumor demonstrated by ultrasonography (US) or contrast-enhanced computed tomography (CT) at one month after surgery. Diagnosis of HCC was confirmed by at least two pathologists. This study was approved by the Institutional Ethics Committee of the Affiliated Drum Tower Hospital of Nanjing University Medical School. The principles outlined in the *Declaration of Helsinki* were followed.

Follow-up

The patients were followed up regularly in our outpatient clinic. Monthly serum alpha-fetoprotein (AFP) tests were conducted in the first three months postoperatively. Regular serum AFP, chest X-ray and abdominal US or contrast-enhanced CT was done at least every three months in the first two years. The patients were followed up every six months during the 3rd to 5th years. After five years, the patients were asked to visit outpatient clinic annually. Recurrence was diagnosed when recurrent tumor was confirmed by imaging. Recurrence within two years after surgery was determined as early recurrence.[5, 10]

Analyzed parameters

The parameters included in the analysis were categorized into patient characteristics, preoperative liver function markers, surgical factors and tumor-related factors. Patient characteristics included gender, age, body mass index (BMI), hypertension, diabetes, smoking, and alcohol consumption. Status and type of hepatitis were recorded. HBV DNA was quantitatively determined and analyzed in HBV-infected patients.

Preoperative serum liver enzyme tests were regularly conducted. Parameters used in this analysis included alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), γ-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), direct bilirubin (DBIL), cholinesterase (CHE), albumin (ALB), prothrombin time (PT), international normalized ratio (INR) and AST/ALT ratio. The status of cirrhosis, portal hypertension and detectable ascites were examined. The diagnosis of portal hypertension was established according to the criteria of Barcelona Clinic Liver Cancer (BCLC) group defined as the presence of either esophageal varices detected by endoscopy or splenomegaly (major diameter >12 cm) with platelet count less than 100 000/mm^3.[11] Child-Turcotte-Pugh (CTP) classification and Model for End-stage Liver Disease (MELD) score were also evaluated.

Surgical factors subjected to analysis included the use of vascular occlusion, total blood loss, blood transfusion, and the distance from resection margin to tumor. Hepatectomies involving three or more segments were defined as major resections. Liver resections of less than three segments, wedge resections or tumor enucleations were defined as minor resections.

Tumor related clinicopathologic factors that potentially associated with HCC recurrence were analyzed. The parameters included preoperative serum AFP level (upper limit in our hospital: 5 ng/mL), size of tumor, number of tumor, tumor capsule, microvascular invasion, macrovascular invasion, adjacent organ invasion and differentiation of HCC (categorized by poor/moderate/well or Edmonson-Steiner grade I-II/III-IV). TNM staging was performed according to the *American Joint Committee on Cancer Staging Manual* (7th edition). BCLC stage was determined as previously described.[12]

Statistical analysis

Univariate analysis was used to identify potential risk

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