Preoperative inflammation-based markers predict early and late recurrence of hepatocellular carcinoma after curative hepatectomy

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BACKGROUND: Recurrence of hepatocellular carcinoma (HCC) after curative resection remains a major cause of treatment failure and tumor-related death. Patterns of HCC recurrence can be categorized into early recurrence and late recurrence which have different underlying mechanisms. In this study, we investigated if simple inflammation-based clinical markers can distinguish patterns of recurrence after curative resection of HCC.

METHODS: A retrospective analysis of 223 patients who underwent curative hepatectomy for HCC was performed. Preoperative inflammation-based factors including neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio, γ-glutamyl transferase/alanine aminotransferase ratio, aspartate aminotransferase/platelet ratio index (APRI) and prognostic nutritional index together with other clinicopathologic parameters were evaluated by univariate analysis and multivariate analysis to identify independent prognostic factors. By combining risk factors, predictive models were established to distinguish populations at high risk of early or late recurrence.

RESULTS: Age ≤50 years, resection margin ≤1 cm, TNM stage III-IV, NLR>2.75, APRI>0.23 and positive alpha-fetoprotein were independent adverse prognostic factors for early recurrence. Patients with three or more risk factors were at significant higher risk of early recurrence. APRI>0.23 and positive hepatitis B e antigen (HBeAg) were independent risk factors of late recurrence, the coexistence of high APRI and positive HBeAg increased the risk of late recurrence.

CONCLUSIONS: Preoperative inflammation-based prognostic factors predict early and late recurrence of HCC after curative resection. Different prognostic factor combinations distinguish high-risk populations of early or late HCC recurrence.

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KEY WORDS: hepatocellular carcinoma; inflammation; prognosis; recurrence; hepatectomy

Introduction

Despite recent improvement in the treatment of hepatocellular carcinoma (HCC), the prognosis of this deadly disease remains poor.[1, 2] To date, surgical resection of HCC has become a safe procedure with a low mortality rate.[3] However, high incidence of recurrence remains a major cause of death after curative resection.[4, 5] The recurrence of HCC could originate from either intrahepatic metastasis of primary tumor or *de novo* tumor arising from the remnant liver.[5] This notion is supported by different patterns of recurrence observed: early recurrence (<1 year after surgery) and late recurrence (>1 year).[6] Identified risk factors also indicate that early recurrence is mainly associated with invasive tumor characteristics whereas late recurrence is largely contributed by continuous liver disease.[5, 7] Understanding and predicting recurrence pattern may help improve the outcome of HCC.

Recent research reveals that inflammation facilitates HCC malignant behavior and is correlated with poor prognosis.[8] Inflammation participates in the process of liver carcinogenesis, tumor growth and metastasis through various molecular pathways.[8] However, these molecular markers are not readily observable in daily medical practice. Several inflammation-based scores or indices derived from simple clinical tests are proposed to serve as prognostic predictors of cancer patients. Neutrophil/lymphocyte ratio (NLR), as a systemic inflammation

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index, is associated with the prognosis of many cancers including HCC.[9, 10] Another inflammation-based marker platelet/lymphocyte ratio (PLR) also has prognostic value in HCC patients receiving transplantation.[11] Moreover, prognostic nutritional index (PNI) and aspartate aminotransferase (AST)/platelet ratio index (APRI) incorporate inflammation markers and variables indicating nutrition status or liver function. They also have significant prognostic value in HCC patients.[12, 13] Based on common liver enzymes, elevated γ-glutamyl transferase/alanine aminotransferase ratio (GGT/ALT) reflects liver inflammatory microenvironment and correlates with poor prognosis of HCC.[14, 15] However, potential relationship between these inflammation-based prognostic markers and HCC recurrence patterns has not yet been elucidated.

Therefore, the present study investigated whether preoperative inflammation-based markers predict early and late recurrence patterns in patients undergoing curative resection of HCC.

Methods

Patients

The data of patients who had undergone hepatectomy for HCC at the Department of Hepatobiliary Surgery, the Affiliated Drum Tower Hospital of Nanjing University between July 2004 and April 2011 were retrieved from a prospectively maintained database and were analyzed retrospectively. Only patients with complete follow-up information and required clinicopathologic data were included. Patients with evidence of infection or systemic inflammatory diseases were excluded. Curative hepatectomy was defined as complete removal of HCC without grossly and microscopically identifiable tumor residue on resection margin. Among the 223 patients analyzed, 77 underwent left hemihepatectomy, right hemihepatectomy or central bisectionectomy, and 87 underwent segmentectomy, bisegmentectomy or trisegmentectomy. The other 59 patients underwent local tumor resection. Anatomical liver resection was performed in 177 patients. Tumor enucleation or atypical liver resection was conducted in 46 patients. Among these patients, three underwent radiofrequency ablation (RFA) before surgery. Twenty received transarterial chemoembolization (TACE) prior to resection. Diagnosis of HCC was based on imaging, serum alpha-fetoprotein (AFP) test and was finally confirmed by at least two experienced pathologists. Systemic chemotherapy or sorafenib was not used after surgery. Thirty-five patients underwent TACE after liver resection as adjuvant therapy. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the *Declaration of Helsinki* 1964 and its later amendments or comparable ethical standards.

Follow-up

Follow-up was conducted regularly in outpatient clinic of our hospital. Monthly serum AFP test was performed during the first three months after surgery. Chest X-ray, abdominal ultrasonography (US) or contrast-enhanced computed tomography (CT) was regularly performed at least every three months in the first two years. After that, patients were followed up and received serum and imaging examination every six months during the third to fifth years. Five years afterwards, the follow-up was carried out annually. Tumor recurrence was diagnosed by imaging and laboratory tests. The median follow-up period was 26.1 months (range 1.9-72.6). Recurrence within one year after surgery was defined as early recurrence.[5, 16] For the treatment of HCC recurrence, TACE was the most frequently used treatment of recurrent HCC. Forty-nine patients with early recurrence and 21 with late recurrence underwent TACE treatment. RFA was performed in 18 early recurrence and 18 late recurrence patients. Eight patients with early recurrence underwent recurrent tumor resection and one patient received liver transplantation. For late recurrence, 11 patients underwent surgical resection. Patients who were unsuitable for invasive treatment received best supportive care.

Inflammation-based markers and other variables

Inflammation-based scores were calculated using preoperative data from whole blood cell count and liver function test. TNM staging was performed according to the *American Joint Committee on Cancer staging manual* (7th edition). Barcelona Clinic Liver Cancer (BCLC) staging was determined as previously described.[17] The status of tumor was also assessed by the Milan criteria (single lesion ≤5 cm in diameter or up to 3 nodules ≤3 cm in each diameter, no extrahepatic metastasis, no vascular invasion).[18] Liver function was evaluated by Child-Turcotte-Pugh (CTP) classification and Model for End-stage Liver Disease (MELD) score.

Statistical analysis

Continuous variables were dichotomized by normal limits of laboratory tests or cut-off values determined by receiver-operating characteristics (ROC) analysis. The cut-off values were determined by seeking the maximal sum of sensitivity and specificity. Recurrence-free survival (RFS) rates were evaluated by the Kaplan-Meier method. RFS between groups was compared by the log-rank test. Univariate and multivariate analysis were performed by the Cox proportional hazard model. Parameters with