Patients with early recurrence of hepatocellular carcinoma have poor prognosis

Tomoki Kobayashi, Hiroshi Aikata, Tsuyoshi Kobayashi, Hideki Ohdan, Koji Arihiro and Kazuaki Chayama

Hiroshima, Japan

BACKGROUND: Early recurrence (ER) after hepatic resection (HR) is a poor prognostic factor for patients with hepatocellular carcinoma (HCC). This study aimed to identify the clinicopathological features, outcomes, and risk factors for ER after HR for small HCC in order to clarify the reasons why ER is a worse recurrence pattern.

METHODS: We retrospectively examined 130 patients who underwent HR for small HCC (≤30 mm). Recurrence was classified into ER (<2 years) and late recurrence (LR) (≥2 years). The clinicopathological features, outcomes, and risk factors for ER were analyzed by multivariate analysis.

RESULTS: ER was observed in 39 patients (30.0%). The survival rate of the ER group was significantly lower than that of the LR group (P<0.005), and ER was an independent prognostic factor for poor survival (P=0.0001). The ER group had a significantly higher frequency (P=0.0039) and shorter interval (P=0.027) of development to carcinoma beyond the Milan criteria (DBMC) compared with the LR group, and ER was an independent risk factor for DBMC (P<0.0001). Multi-nodularity, non-simple nodular type, and microvascular invasion were independent predictors for ER (P=0.012, 0.010, and 0.019, respectively).

CONCLUSIONS: ER was a highly malignant recurrence pattern associated with DBMC and subsequent poor survival after HR for small HCC. Multi-nodularity, non-simple nodular type, and microvascular invasion predict ER, and taking these factors into consideration may be useful for the decision of the treatment strategy for small HCC after HR.

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KEY WORDS: early recurrence; small hepatocellular carcinoma; risk factors; beyond the Milan criteria

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and it ranks sixth in cancer incidence and third in cancer mortality worldwide.[1] The establishment of surveillance for patients at high risk of HCC, such as those with hepatitis B or C virus (HBV/HCV) infection and liver cirrhosis, and recent advances in diagnostic modalities, have led to an increased detection rate of tumors at an early stage. Specifically, these tumors are solitary and small, and they represent an opportunity for radical treatment.[2-4] However, the prognosis of HCC patients remains poor because of the high incidence of recurrence, even in patients with small HCC.[5] Thus, it is critical in the management of HCC to predict recurrence patterns (interval until postoperative recurrence) before treatment decisions are made and to identify their mechanisms because the prognosis of recurrent HCC after hepatic resection (HR) strongly depends on recurrence patterns.[5-10] Therefore, strategies based on recurrence patterns should be considered in order to improve the prognosis of HCC patients.

Recurrence of HCC is thought to have two main mechanisms: one is intrahepatic metastasis (IM) from the primary tumor caused by dissemination of tumor cells in the portal vein, and the other is *de novo* multi-

Author Affiliations: Department of Gastroenterology and Metabolism (Kobayashi To, Aikata H and Chayama K), and Department of Anatomical Pathology (Arihiro K), Hiroshima University Hospital, Hiroshima, Japan; Department of Gastroenterological and Transplant Surgery, Applied Life Sciences, Institute of Biomedical and Health Sciences (Kobayashi Ts and Ohdan H), and Liver Research Project Center (Chayama K), Hiroshima University, Hiroshima, Japan

Corresponding Author: Hiroshi Aikata, MD, PhD, Department of Gastroenterology and Metabolism, Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan (Tel: +81-82-257-5192; Fax: +81-82-257-5194; Email: aikata@hiroshima-u.ac.jp)

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centric carcinogenicity as a result of persistent hepatitis and fibrosis in the remnant liver.[7] Early recurrence (ER) within 2 years after HR is mainly related to IM and is associated with aggressive tumor biology.[7-9] Further, ER is the leading cause of early death after HR[5, 8] and the interval from HR to recurrence is an independent prognostic factor for survival after recurrence.[6] On the other hand, late recurrence (LR) more than 2 years after HR is mainly related to multicentric carcinogenicity and is associated with a background of chronic inflammatory liver disease and cirrhosis.[7] LR has a relatively good prognosis because of the establishment of effective treatments for underlying liver disease and cirrhosis, namely, anti-viral therapy for HBV and HCV, such as interferon (IFN) therapy,[10, 11] nucleoside analogue (NA) therapy,[12] and direct-acting antiviral agents (DAAs). Furthermore, most patients with LR have carcinoma within the Milan criteria and many treatment options are available such as re-resection, percutaneous ablation therapy, and salvage liver transplantation (LT).[13] Accordingly, the strategies for ER may be the key to improving the prognosis of HCC patients, and the identification of clinicopathological features and risk factors for ER may be useful for guiding the management of HCC. On the other hand, it is unclear why ER is a worse recurrence pattern, and so far, no study has investigated the reasons for this, although ER is well known as a poor prognostic factor.

The aim of this study was to identify the clinicopathological features, outcomes, and risk factors for ER after HR for small HCC. In particular, we focused on the differences of clinical course after recurrence (recurrence features) between the ER and LR groups in order to clarify the reasons why ER is a worse recurrence pattern.

Methods

Patients

Five hundred thirty-seven HCC patients who received curative HR as initial treatment at Hiroshima University Hospital between October 2003 and November 2012 were considered as candidates for this study. Curative HR was defined as resection of all macroscopic residual tumors. Inclusion criteria were as follows: (1) diagnosis of HCC confirmed by typical radiological imaging (the tumor demonstrates hepatic arterial enhancement and fades during the portal venous and equilibrium phases) along with postoperative pathological examination; (2) no radiological evidence of vascular invasion or extrahepatic metastasis; (3) tumors ≤30 mm in maximum diameter; (4) tumor number ≤3; and (5) no preoperative treatment for HCC such as transarterial chemoembolization (TACE) or radiofrequency ablation (RFA). In patients with multiple HCCs, the largest tumor was analyzed. Finally, 130 patients met these criteria and were enrolled (Fig. 1). This study did not require approval from the institutional ethics committee or informed consent, and complied with the principles of *the Declaration of Helsinki*.

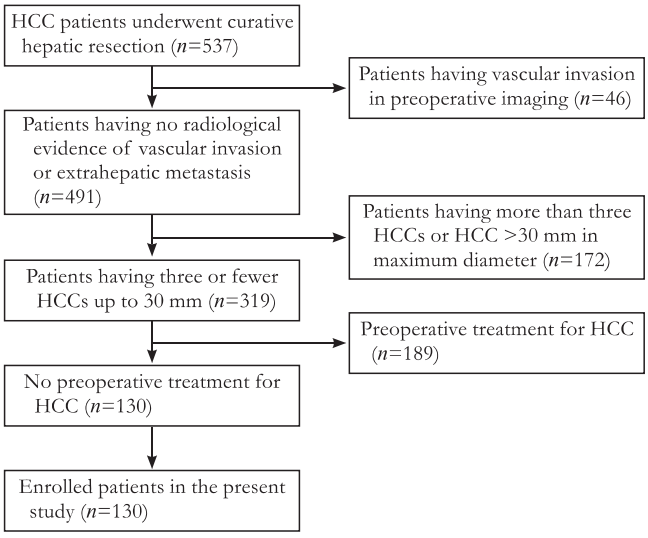

Fig. 1. Flow chart of the patient selection process in this study.

Clinicopathological variables

Data on clinicopathological variables such as age, gender, etiology of liver disease, presence or absence of cirrhosis, Child-Pugh classification, platelet count, alanine aminotransferase (ALT), total bilirubin (T-Bil), prothrombin time (PT), albumin (Alb), indocyanine green retention rate at 15 minutes (ICG-R15), α-fetoprotein (AFP), lens culinaris agglutinin A-reactive AFP (AFP-L3), des-γ-carboxy-prothrombin (DCP), surgical procedure, tumor size, tumor number, macroscopic classification, tumor differentiation, intrahepatic micrometastasis, microvascular invasion (MVI), surgical margin, and tumor stage were obtained and analyzed. All tumor-related factors were determined by pathological assessment of resected tissue. We defined tumor size as the maximum diameter of the resected tumor specimen. When different tumor grades were found within the same tumor, the predominant grade was used in the analysis. Macroscopic classification was divided into five types according to the classification of the Liver Cancer Study Group of Japan (LCSGJ):[14] (i) small nodular type with indistinct margins (SN-IM), (ii) simple nodular type with distinct margins (SN-DM), (iii) simple nodular type with extranodular growth (SN-EG), (iv) confluent multinodular type (CMN), and (v) infiltrative type (IF). Further, SN-IM and SN-DM were grouped as simple nodular (SN)-type, and SN-EG, CMN and IF as non-simple nodular (non-SN)