

# Risk factors associated with early and late recurrence after curative resection of hepatocellular carcinoma: a single institution's experience with 398 consecutive patients

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**BACKGROUND:** Surgical resection is an important curative treatment for hepatocellular carcinoma (HCC); however, some patients experience an unexpected recurrence even after hepatectomy. The present study aimed to investigate risk factors and predictive criteria for early and late recurrence of HCC after resection.

**METHODS:** A retrospective analysis of 398 Chinese patients who received curative resection for HCC was conducted. Patients were divided into three groups: without recurrence, early recurrence, and late recurrence. Prognostic factors and predictive criteria for early and late recurrence were statistically analyzed.

**RESULTS:** The cumulative recurrence-free survival rates at 1, 2, 3, 4, and 5 years were 75.5%, 58.2%, 54.1%, 40.5%, and 28.7%, respectively. The distribution of the time to recurrence suggested that recurrence could be divided into early phase (before 2 years;  $n=164$ ) and late phase (after 2 years;  $n=83$ ). Cox's multivariate proportional hazard model analysis revealed that multiplicity of tumors ( $P=0.004$ ) and venous infiltration ( $P=0.002$ ) were independent risk factors associated with early recurrence. In contrast, indocyanine green retention rate at 15 minutes ( $P=0.007$ ), serum albumin level ( $P=0.045$ ), and HBeAg status ( $P=0.028$ ) proved to be significant independent adverse prognostic factors for late recurrence. Patients with at least 1 of the 2 early recurrence risk factors (multiplicity of tumors  $\geq 2$  and venous infiltration) or with 2 or more late recurrence risk factors are often susceptible to recurrence ( $P=1.36e-4$  and  $1.0e-6$ , respectively).

**CONCLUSIONS:** Early and late recurrences correlate with different risk factors and predictive criteria. Early recurrence primarily results from intrahepatic metastases, while late recurrence may be multicentric in origin.

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**KEY WORDS:** hepatocellular carcinoma; intrahepatic recurrence; hepatectomy; risk factors; prognosis

## Introduction

Hepatocellular carcinoma (HCC), a common malignancy worldwide, accounts for approximately one million deaths with an increasing trend of new incidences annually<sup>[1, 2]</sup> and a 5-year survival rate of less than 5% without treatment.<sup>[3]</sup> Surgery, including liver transplantation (LT) and hepatectomy, is the most effective modality for the treatment of patients with HCC.<sup>[4, 5]</sup> However, due to the lack of donor organs, long waiting period, higher perioperative risk, and long-term immunosuppression associated with LT, hepatectomy is widely accepted as the first treatment option for many HCC patients.<sup>[6]</sup> As surgical techniques and perioperative management of patients with HCC have improved, HCC can be resected safely with very low operative morbidity and mortality rates.<sup>[7]</sup> Even after surgical resection, however, the long-term prognosis remains poor due to a high incidence of recurrence (68%-96%),<sup>[8, 9]</sup> making effective therapeutic strategies aimed at controlling tumor recurrence critical for prolonging survival after HCC resection.

To date, various factors influencing the recurrence of HCC have been reported, including tumor-related

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factors,<sup>[10-13]</sup> host liver-related factors,<sup>[14, 15]</sup> and even the type of surgery (e.g., major or minor resections, anatomical or non-anatomical resections, wide or narrow surgical margins, etc.).<sup>[16-18]</sup> Nevertheless, the causes of recurrence, intrahepatic metastasis or multicentric occurrences, remain controversial. In the study, we investigated the time of recurrence and a number of potential predictors to clarify the prognostic factors and predictive criteria of early and late recurrence in patients who underwent a curative partial hepatectomy for HCC.

## Methods

### Patients

Between March 2007 and January 2011, 572 patients underwent resections of HCC at the Department of Liver and Vascular Surgery, West China Hospital of Sichuan University. Of these patients, 174 were excluded from the present study. Two died in the hospital during the operation period; 79 received other treatments before admission to undergo hepatectomy, and another 86 underwent intraoperative ablation because of multinodularity with some nodules left unresected. In addition, the other 7 patients were excluded because of positive macroscopic or microscopic margin ( $n=5$ ) or disease detected in the liver remnant by ultrasonography or contrast-enhanced CT at 1 month after hepatectomy ( $n=2$ ), which was considered a residual disease. After these exclusions, 398 patients who had undergone curative resection were enrolled in this study. Curative resection was defined as complete excision of the tumor and macroscopic portal vein tumor thrombi with a clear microscopic margin (R0 resection) and no residual tumors demonstrated by ultrasonography or contrast-enhanced CT at 1 month after surgery. All the patients in this study underwent a preoperative indocyanine green (ICG) excretive test which has been described in detail elsewhere.<sup>[19, 20]</sup> Patients who received preoperative and postoperative anti-hepatitis B therapy were recorded and the relationship between anti-hepatitis B therapy and late recurrence was analyzed.

The study protocol for collecting and using human samples was approved by the Institutional Ethics Committee of our hospital. Written informed consent was obtained from all participants involved in this study.

### Surgical modalities

Table 1 shows the types of hepatectomy performed. A resection was defined as "major" if 3 or more segments were removed, according to Couinaud's classification. Major hepatectomies were performed in 207 patients

**Table 1.** Types of hepatectomy

Types	Data (n, %)
Major hepatectomy	207 (52.0)
Right trisegmentectomy	64 (16.1)
Right hepatectomy	48 (12.1)
Left hepatectomy	42 (10.6)
Extended right hepatectomy	19 (4.8)
Extended left hepatectomy	14 (3.5)
Others*	20 (5.0)
Minor hepatectomy	191 (48.0)
Left lateral segmentectomy	51 (12.8)
Bisegmentectomy VI and VII	32 (8.0)
Bisegmentectomy V and VIII	25 (6.3)
Segmentectomy	26 (6.5)
Nonanatomical wedge resections or enucleations	57 (14.3)

\*: including 20 patients with 3 or more discontinuous segments resected.

(52.0%), including 20 (5.0%) patients with 3 or more discontinuous segments resected. One hundred and ninety-one patients (48.0%) underwent minor hepatectomies that were predominantly non-anatomical wedge resections ( $\leq$ two segments) or enucleations (57, 14.3%), and left lateral segmentectomy (51, 12.8%). The average number of hepatic segments resected was  $3.2 \pm 0.4$  (range 0-6). Anatomical resection (AR), defined as any type of systematic resection of the portal regions based on Couinaud's classification, was performed in 299 patients (75.1%), while non-anatomical resection (non-AR) was performed in 99 (24.9%). In this study, incomplete removal of the tumor-bearing portal regions, such as wedge resection or enucleation, was classified as a non-AR, while discontinuous segments resection was included in AR, if every resection in that patient was AR; if not, then it was considered non-AR.<sup>[21]</sup>

### Diagnosis of HCC

HCC was detected by contrast ultrasonography, dynamic CT and MRI. A focal lesion ( $\leq 2$  cm in diameter) with arterial hypervascularization and venous washout detected by 2 imaging techniques or a single imaging modality associated with a focal lesion  $> 2$  cm in diameter was suggestive of HCC.<sup>[22]</sup> All HCC diagnoses were confirmed histopathologically after resection. Pathological grading was based on the Edmondson-Steiner criteria.<sup>[23]</sup>

### Follow-up

All patients were seen regularly in the outpatient clinic and monitored prospectively for recurrence by a standard protocol. Follow-up consisted of monthly blood tests for monitoring serum alpha-fetoprotein level and ultrasonography or contrast-enhanced CT at least once

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