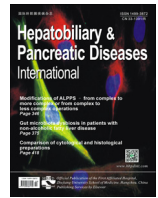




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Original Article/Liver

## Prognostic value of postoperative complication for early recurrence after curative resection of hepatocellular carcinoma

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## ABSTRACT

**Background:** Postoperative complications may adversely affect oncological outcomes. The aim of this study was to evaluate the impact of postoperative complications on early-phase recurrence after curative resection for hepatocellular carcinoma (HCC).

**Methods:** We included 145 HCC patients who underwent initial and curative resection between January 2004 and December 2013. Postoperative complications of grade III or higher based on Clavien–Dindo classification were defined as clinically relevant postoperative complications. Recurrence within two years after hepatectomy was defined as early-phase recurrence.

**Results:** Thirty-eight patients (26%) developed postoperative complications. The only predictive factor for postoperative complication was longer operative duration ( $P=0.037$ ). The disease-specific survival rate of patients with complication was lower than that of patients without complications ( $P=0.015$ ). Early-phase recurrence was observed in 20/38 (53%) patients who suffered postoperative complications and 36/107 (34%) patients with no complications, which was statistically significant ( $P=0.039$ ). Multivariate analysis identified four factors contributing to early-phase recurrence: high serum AFP level ( $P=0.042$ ), multiple tumors ( $P<0.001$ ), poor differentiation ( $P=0.036$ ) and presence of postoperative complication ( $P=0.039$ ).

**Conclusions:** Postoperative complication is an independent prognostic factor for early-phase recurrence after curative resection of HCC. Close observation of patients with postoperative complications may be a necessary treatment strategy for HCC.

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## Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death worldwide [1,2]. Although hepatic resection is a curative treatment, postoperative long-term prognosis remains poor because of high tumor recurrence, which is observed in 60–70% of cases within five years after operation [3–6]. The most common site of recurrence is the residual liver, which may reflect intrahepatic metastasis from the initial tumor or the development of *de novo* tumors [6–9]. Although it is usually difficult to distinguish intrahepatic recurrence from *de novo* HCC, recently, the duration from surgery to the appearance of secondary tumors has been recognized as an indicator to distinguish intrahepatic metastasis from

*de novo* tumors. Liver tumors developing within two years after surgery are believed to be intrahepatic metastases [10].

Postoperative complications adversely affect oncological outcomes in various cancers [11,12]. Regarding HCC, postoperative complications were observed among 30.9–42.6% of patients after resection [13–15]. Several studies have confirmed the negative impact of postoperative complications on long-term survival in patients with HCC after curative resection [16,17]. However, few studies discuss the effects of recurrence after curative resection. Recurrence after curative resection of various cancers results from occult micrometastasis. In comparison, the appearance of secondary tumors in the residual liver after curative resection for HCC occurs not only from micrometastasis but also from the development of *de novo* tumors. Therefore, the impact of postoperative complication on recurrence from occult micrometastasis should be evaluated differently from other cancers. Thus, the aim of this study was to evaluate the impact of postoperative complications on early-phase in HCC.

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## Methods

### Patients

We examined the medical records of consecutive patients undergoing hepatic resection of primary hepatic cancer at Tottori University Hospital from January 2004 to December 2013. A total of 211 patients with histologically diagnosed HCC underwent hepatectomy, 145 patients underwent an initial and curative hepatectomy. Operative indications included the following factors: performance status <3, preserved liver function estimated from both indocyanine green test and volumetric computed tomography, and good general condition without serious organ failure. Non-anatomical hepatectomy was performed for patients who were estimated to have insufficient volume of remnant liver or who had tumors located peripherally. Intraoperative temporary inflow clamping and transfusion were performed on demand from the operator, and anesthesiologists in charge, respectively. Curative resection was defined as complete macroscopic removal of tumors for which preoperative study had revealed no extrahepatic lesions or invasion to main hepatic vessels, including the intrahepatic portal vein, hepatic vein, and intrahepatic biliary duct. Patients who had undergone liver transplantation or surgical resection combined with ablation therapy were excluded. In this study, patients were divided into two groups: the complication group, which included patients with  $\geq$ Clavien–Dindo grade III complications, and the no complication group, which included patients without complications or with grade I or grade II complications.

Written informed consent was obtained from all patients prior to surgery. Medical records were reviewed retrospectively after approval by the Institutional Review Board of our institution in accordance with the ethical standards laid down in the 1964 *Declaration of Helsinki* and its later amendments (1606A029).

### Variables

The data included patient characteristics [age, gender, body mass index (BMI), comorbidity, cause of hepatitis, Child–Pugh score, serum creatinine, albumin, and cholinesterase levels]; tumor characteristics (number of tumors, maximum tumor diameter, and alpha-fetoprotein (AFP) level); intraoperative data (extent of resection, usage of intermittent total hepatic inflow clamping, duration of surgery, intraoperative hemorrhage volume, amount of intraoperative blood transfusion, length of hospital stay after surgical resection, and postoperative complications); and tumor pathological findings (capsule formation, microscopic vascular invasion, tumor differentiation, and stage of fibrosis of nontumor-bearing liver according to the new Inuyama classification of chronic hepatitis [18]). Patients were followed up every 3–6 months via liver function tests, tumor marker measurements, and an imaging examination with computed tomography (CT) and/or magnetic resonance imaging (MRI). Comorbidity of cardiovascular disease was identified when patients had past history of angina pectoris or chronic heart failure. Disease recurrence and patient survival duration data were collected from our database. Major resection was defined as including more than two Couinaud segments. Tumor recurrence was diagnosed based on the findings of either CT or MRI, which was routinely performed every 6 months. Extrahepatic recurrence was defined as recurrence that included only extrahepatic metastasis without intrahepatic recurrence. Early-phase recurrence was defined as recurrence diagnosed within two years after operation and late-phase recurrence meant recurrence diagnosed two years after operation [10].

**Table 1**

Details of postoperative complications according to Clavien–Dindo classification ( $n = 145$ ).

	Grade of complication			Total	
	III		IV		
	IIIa	IIIb	IVa		
Bile leakage	9	4	0	13 (9%)	
Abdominal abscess	7	0	0	7 (5%)	
Pleural effusion	7	0	0	7 (5%)	
Bile duct stricture	2	2	0	4 (3%)	
Liver failure	2	0	0	1 (2%)	
Pneumonitis	1	0	1	2 (2%)	
Urethral injury	1	0	0	1 (1%)	
Wound disruption	0	1	0	1 (1%)	
Total	36 (25%)		1 (1%)	1 (1%)	38 (26%)

### Statistical analysis

The primary endpoint of this study was early-phase recurrence rate, and the secondary endpoints were overall survival rate, disease-specific survival rate, and extrahepatic recurrence rate among the complication and no complication groups. Overall survival and recurrence-free survival (RFS) was determined by Kaplan–Meier analysis. Predictive factors of postoperative complications, extrahepatic recurrence and other factors contributing to early-phase recurrence were investigated using multivariate analysis based on the variables selected by each univariate analysis using a logistic regression model and Cox proportional hazards regression model, respectively. All continuous values are presented as the mean  $\pm$  standard deviation (SD). Statistical analysis was conducted using Chi-square test and Fisher's exact test (contained less than five variables) for categorical variables. Welch's two-sample *t* test was used for continuous variables. A  $P < 0.05$  was considered statistically significant. R version 3.1.3 software ([www.r-project.org/](http://www.r-project.org/)) was used for comparative statistical analysis.

## Results

### Postoperative complications and patients' characteristics

The mean follow-up period of the 145 HCC patients enrolled in this study was 53.8 months. Median overall survival and median RFS of the whole population were 91 months and 32 months, respectively. **Table 1** shows the details of patients' postoperative complications. Thirty-eight patients (26%) developed postoperative complications of grade III or higher according to Clavien–Dindo classification. Bile leakage was the most frequent complication, followed by abdominal abscess and pleural effusion.

**Table 2** shows a comparison of patients' clinicopathological characteristics and operative and postoperative data between the no complication and complication groups. Patients in the complication group had significantly higher frequency of inflow clamping maneuver, longer operative duration and hospital stay compared with those in the no complication group. However, there was no significant difference in demographic and pathological indicators between the two groups. Multivariate analysis indicated that operative duration was an independent risk factor for postoperative complication ( $P < 0.05$ , **Table 3**).

### Survival analysis and the first site of recurrence

**Fig. 1** shows the prognosis of patients with HCC after operation. Overall survival of patients in the complication group tended to be worse than that in the no complication group (**Fig. 1A**,  $P > 0.05$ ). Moreover, disease-specific survival (i.e., death from HCC only) in

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