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Postoperative complications are predictive of poor prognosis in hepatocellular carcinoma



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ABSTRACT

Background: A retrospective study was performed at some high-volume institutions to clarify the prognostic significance of postoperative complications in patients who had undergone hepatectomy for hepatocellular carcinoma (HCC). No published studies have investigated the relationship between postoperative complications of Clavien–Dindo grade III or more and prognosis in patients who have undergone hepatic resection.

Methods: Patient data were retrospectively collected for 966 consecutive patients who had undergone hepatectomy for HCC with curative intent between January 2004 and December 2012. The patients were assigned to two groups according to the presence of postoperative complications. Clinicopathologic, surgical outcome, and long-term survival data were analyzed.

Results: Hospital deaths occurred in nine patients (0.9%). Postoperative complications were identified in 165 patients (17.1%). Compared with patients without complications, patients with complications had significantly larger tumors, more advanced-stage tumors, more poorly differentiated tumors, more intrahepatic metastasis, longer operation time, greater blood loss, more blood transfusion, and more anatomic resection and combined resection. The overall 5-y survival rates were 48.6% in patients with postoperative complications and 73.2% in patients without them. The 5-y recurrence-free survival rates were 23.7% in patients with postoperative complications and 36.7% in patients without them. Multivariate analysis revealed that longer operation time and lower serum albumin level of albumin were independent predictive factors for occurrence of postoperative complications.

Conclusions: In patients with HCC, posthepatectomy complications are predictive of a worse overall survival, even when adjustments have been made for other known predictors.

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world [1,2]. Because HCC is usually associated with liver cirrhosis and therefore a bleeding tendency, hepatectomy in patients with HCC tends to be a dangerous procedure. Although there have been many improvements in perioperative morbidity and mortality over the past 20 y, relatively high morbidity rates associated with hepatectomy for HCC remain problematic [3–8].

Postoperative complications may lead to systemic inflammation, and there is increasing evidence that increased systemic inflammation correlates with adverse effects on the short- and long-term outcomes of various cancers [8–11]. For example, a high serum C-reactive protein level or neutrophil-to-lymphocyte ratio has been shown to be associated with poorer survival after hepatic resection [12,13]. The mortality rate of hepatectomy in patients with liver cirrhosis was 58% in 1977 [7]. Chok *et al.* [8] reported that postoperative complications affected overall survival after hepatectomy for HCC in a series between December 1989 and December 2004. This large series (863 patients) was from a single center in which the morbidity was 33.4%. The mortality rate has decreased in more recent years.

Postoperative complications are distressing for patients and medical staff and leads to higher medical costs. Therefore, identification of predictors of posthepatectomy complications is needed. A retrospective study was performed at some high-volume institutions to investigate the outcomes of patients with postoperative complications who had undergone hepatic resection for HCC. The outcomes of these patients were compared with those of patients without postoperative complications who had undergone hepatic resection during the same period.

2. Methods

2.1. Patient characteristics

From January 2004–December 2012, 273 patients at the Department of Surgery II, Kyushu University, 346 patients at the Department of Surgery, Hiroshima Red Cross Hospital, and 347 patients at the Department of Surgery, Iizuka Hospital underwent hepatic resection for HCC. In all, 966 patients (660 men and 306 women) were enrolled in this study. Their mean age was 68 y, and the median follow-up was 3.4 y. Curative resection was defined as complete macroscopic removal of tumor. Patients who had undergone hepatic resection combined with ablation therapy were included.

The following possible predictors were assessed with respect to overall and recurrence-free survival: age; sex (male *versus* female); hepatitis B surface antigen (HBs Ag; HBs Ag[+] *versus* HBs Ag[-]), hepatitis C (HCV) antibody (HCV[+] *versus* HCV[-]); body mass index (BMI); diabetes mellitus (absence *versus* presence); serum albumin level; serum total bilirubin; serum bilirubin level; serum aspartate aminotransferase level; platelet count; creatinine; indocyanine green retention test at

Table 1 – Type of postoperative complication over Dindo–Clavien complication grade III.

Complication	Number of patients
Brain	2 (0.2)
Cardiac	2 (0.2)
Pulmonary	
Effusion	21 (2.1)
Pneumonia	5 (0.5)
Gastrointestinal	
Bile leakage	33 (3.4)
Intra-abdominal abscess	28 (2.9)
Ascites	17 (1.7)
Liver failure A/B/C*	2/3/4 (0.9)
Cholecystitis	3 (0.3)
Perforation	2 (0.2)
Gastrointestinal bleeding	2 (0.2)
Ileus	1 (0.1)
Abdominal hemorrhage	1 (0.2)
Urinary tract infection	1 (0.1)
Renal failure	1 (0.1)
Wound infection	29 (3.0)
Bone fracture	2 (0.2)

* Liver failure A,B,C were defined according to the criteria of the International Study Group of Liver Surgery.

15 min (ICGR₁₅); Child classification (A *versus* B); histologic liver cirrhosis (normal liver + chronic hepatitis *versus* liver fibrosis and liver cirrhosis); tumor size; tumor number (solitary *versus* multiple); TNM stage according to the Liver Cancer Study Group of Japan [13] (I + II *versus* III + IV); tumor differentiation (well differentiated + moderately differentiated *versus* poorly differentiated); microvascular invasion (absence *versus* presence); intrahepatic metastasis (IM; absence *versus* presence); serum alpha-fetoprotein level; des- γ -carboxy prothrombin (DCP); operative time; estimated blood loss; transfusion (absence *versus* presence); operative procedure (anatomic *versus* nonanatomic); ablation therapy; combined resection; length of hospital stay; and hospital death (absence *versus* presence). Patients with diabetes were defined as those using oral hypoglycemic agents or insulin. Patients who had undergone resection of other organs, such as the stomach, colon, or spleen, were defined as the combined resection group. Patients who had required intraoperative ablation therapy such as ethanol injection or radiofrequency ablation were defined as the ablation group. Postoperative complications within 1 mo of hepatectomy included brain infarction, cardiac arrhythmia, heart failure, pleural effusion, pneumonia, liver failure, bile leakage, ascites, ileus, bowel perforation, intraperitoneal abscess, abdominal hemorrhage, gastrointestinal bleeding, cholecystitis, wound infection, urinary tract infection, renal failure, and bone fracture. Complications of grade IIIa or greater according to the Clavien–Dindo classification [14] (those which require surgical intervention) were defined as the presence of postoperative complications. Grade C hyperbilirubinemia and prolonged prothrombin time/international normalized ratio on postoperative day 5 were defined as liver failure, according to the criteria of the International Study Group of Liver Surgery [15]. Any death that occurred in the hospital postoperatively was recorded as a hospital death.

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