Original article

Amount of operative blood loss affects the long-term outcome after liver resection for hepatocellular carcinoma.

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Abstract

Background/Aim: Numerous prognostic factors for HCC have been reported. Few literatures have reported clinical significance of amount of intraoperative blood loss (ABL) for the outcome after surgery for HCC. The aim of this study is to analyze of significance of ABL for outcome after surgery for HCC.

Patients and methods: Total of 301 patients underwent liver resection for HCC between January 1998 and June 2007 were included. Clinical and surgical characteristics were collected and prognostic factors were identified using univariate and multivariate analysis.

Results: Impaired liver function (liver damage B), large tumor (> 36mm), multiple tumors, existence of macroscopic vessel invasion, large ABL (≥ 700ml), and replacement of red blood cell were identified as independent prognostic factors for overall survival (OS). For disease free survival (DFS), old age (> 66), male gender, impaired liver function, large tumor, multiple tumors, existence of macroscopic vessel invasion, and large ABL were extracted. Limited to the patients without blood transfusion, large ABL is associated with poor OS and DFS.

Conclusions: Large ABL could result in poor OS and DFS after liver resection of HCC in patients without blood transfusion. Surgeons have to make the best effort to reduce ABL.

Introduction

Recently, the scene of treatment of HCC has greatly changed. Establishment of antiviral therapy has brought a less occurrence of HCC (1), and radiofrequency ablation therapy has offered satisfactory outcome to a subset of HCC patients (2). However, liver resection has still played a great role as radical option in treatment of HCC. Although innovations of perioperative management and surgical technique have made liver resection much safer, this surgical procedure still includes risk for fatal complication. From the oncological aspect, replacement of blood products could promote recurrence of cancers possibly because of immunosuppressive state (3-5). In the liver surgery, however, there are a few literatures regarding association of amount of blood loss and long-term outcome of operation for HCC (6-8). In this study, we determined the significance of amount of blood loss and blood transfusion for long-tem outcome after resection of HCC.

Patients and methods

Total of 301 patients underwent liver resection for HCC at the Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University from January 1998 to June 2007 were reviewed. Patient's and surgical data including age, gender, status of hepatitis viral infection, liver damage, diameter of tumor, number of tumor, existence of macroscopic vessel invasion, type of liver resection, weight of resected liver, operation time, amount of intraoperative blood loss (ABL), and operation with or without transfusion of red blood cell (RBC) and fresh frozen plasma (FFP) were collected. ABL was defined as total of the amount in suction containers and the weight of laparotomy sponges at the conclusion of operation. Liver damage was categorized according to the fifth edition of The General Rules for

the Clinical and Pathological Study of Primary Liver Cancer (9). Prognostic factors for overall survival (OS) and diseases free survival (DFS) were identified by the univariate and multivariate analysis. According to ABL, patients were divided into large amount of blood loss group (L-ABL) and small amount of blood loss group (S-ABL). ABL of L-ABL was equal to or more than 700ml, and that of A-ABL was less than 700ml. In all patients, OS and DFS were compared between L-ABL and S-ABL. In addition, the same analysis was conducted limited to patients who did not receive replacement of RBC.

OS and DFS were calculated Kaplan-Meier method. Comparison analysis related to OS and DFS was determined by long-rank test. The independent significance of prognostic variables was determined by multivariate analysis using the Cox's proportional hazards model. Only potentially predictive factors on univariate analysis ($P< 0.05$) were entered into the Cox's model. For all statistical analyses, a P value of less than 0.05 was accepted as statistically significant.

Results

The clinical characteristics are summarized in Table 1. There were 250 male and 51 female, with a median age of 64.2 years (range, 30-86). Ninety-nine patients were positive for HbsAg, and 159 were positive for anti-HCV. Of 301 patients, 256 were classified as liver damage A, and the rest were B. Mean tumor size were 46.3mm ranging from 9 to 220mm. Multiple tumor were observed in 129. Perioperative parameters were also listed in Table 1. Anatomical resection was performed in 187. Median ABL was 665ml (range, 15-6000ml). Of 301 patients, 55 received transfusion of RBC and 74 administrated FFP.

The results of univariate analysis for OS and DFS were summarized in Table 2. Liver damage B, large tumor (≥ 36mm in maximum diameter), multiple tumor, existence of macroscopic vessel

invasion, large ABL (≥ 700ml), and operation with transfusion of RBC and FFP were identified as possible prognostic factors for OS by univariate analysis. For DFS, old age (≥ 66), male gender, liver damage B, large tumor, multiple tumor, existence of macroscopic vessel invasion, and ABL ≥ 700ml were extracted. By multivariate analysis, liver damage B (hazard ratio (HR)=2.116, p=0.0032), large tumor (HR=1.856, p=0.0122), multiple tumor (HR=2.288, p=0.0008) and large ABL (HR=1.929, p=0.0453) were identified as independent prognostic factors for OS. Liver damage B (HR=1.850, p=0.0023) and multiple tumors (HR=1.875, p=0.0003) were independent prognostic factors for DFS, and large ABL did not reach to statistical significance (HR=1.407, p=0.0649) (Table 3). Limited to the patients without blood transfusion (n=246), 5-year OS for L-ABL (n=94) and S-ABL (n=152) were 54% and 69 with the statistical significance (p=0.0028). Five-year DFS for L-ABL and S-ABL were 12% and 16%, respectively, and the difference was also statistically significant (p=0.0016) (Fig 1a and 1b).

Discussion

While radiofrequency ablation therapy for HCC has been prevalent worldwide, liver resection is still curative therapeutic option (10,11). Particularly in the treatment of large HCC, surgical resection plays a central role. A number of studies regarding prognostic factors for recurrence of HCC after liver resection have published (12,13). We also have demonstrated the clinical significance of preoperative doubling time of alpha-fetoprotein and protein induced by vitamin K absence for early recurrence and poor outcome of HCC (14). In addition, many molecules have been shown as predictors of recurrence of HCC (15-17). Since these prognostic factors are patient or tumor dependent, however, it is impossible to alter the outcome after liver resection

by surgeons' hand.

Recently, Katz et al reported that operative blood loss was independent predictor for recurrence and survival after resection of HCC (18). Although many reports have demonstrated that blood transfusion could be a significant predictor (19-22), Katz's article is the first one showing the impact of blood loss on recurrence and survival. In that report, they demonstrated a "dose-response" relationship between higher levels of blood loss and disease specific survival. We agree about the part that excessive blood loss is related to recurrence and survival. However, the adverse effect of blood loss on the postoperartive course is not clear because the patients with a large quantity of blood loss are administered replacement of blood products. To clarify the adverse effect of blood loss, the factor of blood transfusion should be eliminated. In the current study, we clearly demonstrated the clinical significance of ABL on the outcome after liver resection for HCC. It is notable result that adverse effect of blood loss was proved in the patients without blood transfusion.

To reduce ABL is an endless challenge for surgeons. We have employed various techniques or surgical devices, such as deep anesthesia with lower central venous pressure (21), reduction of amount of intraoperative drip infusion until completion of dissection of liver parenchyma, surgical patch coated with human fibrinogen and thrombin (23), liver hanging maneuver (24), portal pedicle isolation method, and soft coagulation system for hemostasis. Although it is difficult to elucidate the advantages of each of techniques or surgical devices we employed, the rate of replacement of red blood cell has decreased from 33% to 24% in the recent series of 41 right-side major hepatectomies (submitted data).

Replacement of blood product could induce immunosuppressive state, and could promote

recurrence of HCC. But the explanation for why ABL affects DFS and OS after liver resection is not cleared. Cue et al reported the association between blood loss and immunosuppressive state in hemorrhage model of Lewis rats (25). They demonstrated that hemorrhagic shock and not blood transfusion is a major determinant of the risk of infection. However, patients of large ABL in our series seldom lapsed into hemorrhagic shock state. Although large ABL might include a risk for spillage of tumor cell, the pattern of recurrence in most patients with large ABL was not peritoneal dissemination but intrahepatic recurrence. Extensive peritoneal lavage at the conclusion of operation is possibly able to prevent from establishment of peritoneal dissemination (26). Some kind of immunoresponses can be associated with blood loss (27,28), persuasive evidences have not been demonstrated. Multilateral research should be necessary to clarify the mechanism of disadvantage of ABL against HCC recurrence.

In conclusion, large amount of intraoperative blood loss was an independent prognostic factor for the OS after resection of HCC. This predictive power is valid for patients without any blood transfusion. Liver surgeons have to minimize intraoperative blood loss by precise surgical techniques for the better outcome of the hepatic resection for HCC.

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Table 1. Patients and perioperative characteristics

	n		n
Age		Type of resection	
≥ 66	151	anatomical	187
< 66	150	non-anatomical	114
Gender		WRL¶	
male	250	≥ 190g	144
female	51	< 190g	157
HbsAg		Operation time	
positive	99	≥ 430min	144
negative	202	< 430min	157
Anti-HCV		ABL§	
positive	159	≥ 700ml	150
negative	142	< 700ml	151
Liver damage		Replacement of RBC†	
A	256	yes	55
B	45	no	246
Tumor size		Administration of FFP‡	
≥ 36mm	146	yes	74
< 36mm	155	no	227
Number of tumor			
solitary	172		
multiple	129		
Vessel invasion			
yes	33		
no	268		

¶ WRL, weight of resected liver; § ABL, amount of intraoperative blood loss; † RBC, red blood cell; ‡ FFP, fresh frozen plasma

Table 2. Univariate analysis of patients and perioperative characteristics

	Overall survival		Disease free survival	
	5yr OS	P value	5yr DFS	P value
Age				
≥ 66	57%	0.553	6%	0.016
< 66	51%		31%	
Gender				
male	52%	0.173	18%	0.008
female	64%		30%	
HbsAg				
positive	52%	0.386	25%	0.613
negative	56%		18%	
Anti-HCV				
positive	50%	0.496	17%	0.523
negative	60%		26%	
Liver damage				
A	41%	< 0.0001	21%	0.0007
B	33%		7%	
Tumor size				
≥ 36mm	50%	0.003	14%	0.002
< 36mm	58%		22%	
Number of tumor				
solitary	69%	< 0.0001	31%	< 0.0001
multiple	37%		7%	
Vessel invasion				
yes	40%	0.001	15%	0.031
no	56%		17%	

Table 2 (continued).

	Overall survival		Disease free survival	
	5yr OS	P value	5yr DFS	P value
Type of resection				
anatomical	49%	0.225	21%	0.112
non-anatomical	57%		9%	
WRL[¶]				
≥ 190g	53%	0.057	22%	0.234
< 190g	57%		12%	
Operation time				
≥ 430min	56%	0.078	24%	0.459
< 430min	51%		7%	
ABL[§]				
≥ 700ml	47%	< 0.0001	15%	0.0004
< 700ml	63%		17%	
Tranfusion of RBC[†]				
yes	31%	< 0.0001	20%	0.237
no	59%		19%	
Administration of FFP[‡]				
yes	37%	< 0.0001	24%	0.241
no	60%		18%	

¶ WRL, weight of resected liver; § ABL, amount of intraoperative blood loss; † RBC, red blood cell; ‡ FFP, fresh frozen plasma

Table 3. Multivariate analysis for outcome after liver resection

	Hazard ratio	95% CI	P value
Overall survival			
Liver damage B	2.166	1.296-3.622	0.0032
Tumor size (≥ 36mm)	1.856	1.144-3.009	0.0122
Multiple tumors	2.288	1.409-3.715	0.0008
Vessel invasion (yes)	1.511	0.837-2.726	0.1707
ABL§ (≥ 700ml)	1.929	1.014-3.671	0.0453
Tranfusion of RBC† (yes)	1.587	0.794-3.173	0.1914
Administration of FFP‡ (yes)	0.881	0.436-1.779	0.7235
Disease free survival			
Age (≥ 66)	1.249	0.889-1.755	0.1999
Gender (male)	1.424	0.864-2.347	0.1653
Liver damage B	1.850	1.246-2.747	0.0023
Tumor size (≥ 36mm)	1.321	0.937-1.861	0.1120
Multiple tumors	1.875	1.336-2.631	0.0003
Vessel invasion (yes)	1.136	0.700-7.845	0.6057
ABL§ (≥ 700ml)	1.407	0.979-2.023	0.0649

§ ABL, amount of intraoperative blood loss; † RBC, red blood cell; ‡ FFP, fresh frozen plasma

Figure legends

Fig 1a, Overall survival in the patients without blood transfusion.

Fig 1b, Disease free survival in the patients without blood transfusion.