Negative Impact of Fresh-frozen Plasma Transfusion on Prognosis after Hepatic Resection for Liver Metastases from Colorectal Cancer

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Abstract. *Background: In perioperative management of hepatic resection for colorectal cancer liver metastasis (CRLM), excessive blood loss and blood transfusion greatly influence postoperative complications and prognosis of the patients. We evaluated the influence of the use of blood products on prognosis of patients with CRLM. Patients and Methods: The subjects of this study were 65 patients who underwent elective hepatic resection between January 2001 and April 2011 for CRLM without distant metastasis or other malignancy. We retrospectively investigated the influence of the use of blood products, including red cell concentrate (RC) and fresh frozen plasma (FFP), and clinical variables on overall survival. Results: In univariate analysis, bilobar distribution (p=0.0332), more than four lymph node metastases of the primary cancer (p=0.0155), perioperative RC use (p=0.0205), and perioperative FFP use (p=0.0065) were positively associated with poor overall survival rate. In multivariate analysis, bilobar distribution (p=0.0012), more than four lymph node metastases of the primary cancer (p=0.0171), and perioperative FFP use (p=0.0091), were independent risk factors for poor overall survival rate. Conclusion: The use of FFP is associated with worse overall survival after elective hepatic resection for patients with CRLM.*

Liver metastasis is an important prognostic factor for patients with colorectal cancer, and approximately 25% of patients present with synchronous liver metastases. A further 40-50% of patients develop metachronous colorectal liver metastases (CRLM) within three years of resection of the primary tumor (2). Hepatic resection is the most effective and potentially curative treatment for CRLM (3-6). The 5-year overall survival rate after hepatic resection is reported to range from 28% to 50% (7-11). Inspite of improvements in surgical techniques, instruments, and perioperative management, hepatic resection is still associated with a rather high incidence of blood transfusions that include red cell concentrate (RC), fresh-frozen plasma (FFP), platelet concentrate (PC), and albumin products. Recent studies have reported that allogenic blood transfusion exerts immunomodulatory effects (12-16), and blood transfusion may affect postoperative complications and prognoses of malignancies (17-39). In this study, we retrospectively investigated the relation between perioperative blood transfusion, including RC and FFP transfusion, and overall survival after elective hepatic resection for CRLM.

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Key Words: Blood transfusion, prognosis, colorectal cancer, liver metastasis, hepatic resection.

Patients and Methods

Between January 2000 and April 2011, 88 patients with CRLM underwent first hepatic resection at the Department of Surgery, Jikei University Hospital, Tokyo, Japan. Out of these, 23 patients were excluded, 11 due to other malignancies, 2 due to metastases in other organs, 3 due to peritoneal dissemination, 2 due to non-curative resection, 3 due to liver cirrhosis, 1 because of foam-related pemphigoid, and 1 who was lost to follow-up, leaving the remaining 65 patients for this study. Generally, the extent of hepatic resection was determined based on retention rate of indocyanine green at 15 min (ICG_{R15}) before surgery and hepatic reserve, as described by Miyagawa *et al.* (40), and percutaneous transhepatic portal embolization (PTPE) was performed for patients with estimated residual hepatic volume of less than 30%. The type of resection was classified into two groups: anatomical resection (extended lobectomy, lobectomy, segmentectomy, or subsegmentectomy) and non-anatomical limited partial resection. Since 2003, the use of blood products and dose has been determined by the preference of the attending surgeons based on guidelines for administration of blood products by the Japanese Ministry of Health and Welfare settled in 1999 (41), as well as intraoperative blood loss, postoperative hemoglobin levels, platelet counts, serum albumin, and prothrombin time. We investigated the relation between clinicopathological variables and overall survival after hepatic resection by univariate and multivariate analyses. The factors consisted of the following: age,

Table I. *Patients' characteristics*.

Factor	Mean±SD or ratio	Range
Age (years)	*64.1±10.0	39-85
Gender (male:female)	45:20	
Body mass índex (kg/m^2)	22.2±2.5	15.3-27.6
Procedure (anatomical:partial)	43:22	
Combined resection of the primary cancer (yes:no)	12:53	
Duration of operation (min)	335.8.1±129.7	105-725
Blood loss (g)	1,202.8±1,059.6	30-5,485
Perioperative chemotherapy (yes:no)	44:21	
Post-operative complications (absent:present)	46:19	
Synchronous:metachronous	28:37	
Bilobular:unilobular	13:52	
Number of primary lymph node metastases	1.8±2.1	0-9
Primary cancer (colon:rectum)	40:25	
Serum CEA before hepatic resection (ng/ml)	189.0±441.5	1.9-2,428
RC transfusion (yes:no)	27:38	
FFP transfusion (yes:no)	23:42	

CEA, Carcinoembryonic antigen; RC, red cell concentrate; FFP, fresh-frozen plasma; *mean ± SD.

gender, body mass index (BMI), type of resection, duration of operation, intraoperative blood loss, perioperative chemotherapy, postoperative complications, synchronous or metachronous CRLM, distribution of CRLM, number of regional lymph node metastases of primary colorectal cancer, site of primary tumor, carcinoembryonic antigen (CEA) level before hepatic resection, and perioperative RC or FFP transfusion. Next, in order to assess the risk factors for perioperative FFP transfusion, we investigated on the relation between clinicopathological variables and perioperative FFP transfusion by univariate analyses. The factors were the following 11 variables: age, gender, BMI, type of resection, duration of operation, intraoperative blood loss, synchronous or metachronous CRLM, distribution of CRLM, number of regional lymph node metastases of primary colorectal cancer, site of primary tumor, and serum CEA level before hepatic resection. Clinicopathological continuous variables were classified into two groups for the log-rank test and the Cox proportional hazard regression model as follows: age <65 or ≥65 years, BMI <25 or ≥25 kg/m^2, duration of operation <300 or ≥300 min, intraoperative blood loss <1,000 or ≥1,000 g, number of lymph node metastases of the primary cancer <4 or ≥4, and CEA levels before hepatic resection <20 or ≥20 ng/ml, according to previous studies (6-9). Recurrence of colorectal cancer was defined as newly- detected local, hepatic, lung or extrahepatic tumors by ultrasonogaphy, computed tomography, or magnetic resonance imaging with or without increase in serum CEA or carbohydrate antigen 19-9 (CA 19-9). For recurrent liver metastasis, repeated hepatic resection, local ablation therapy, or systemic chemotherapy was selected based on hepatic functional reserve judged mainly by number, size, and location of the recurrent liver tumors, ICG_{R15} and remnant liver volume. For lung metastasis, limited partial lung resection or systemic chemotherapy was selected. For local recurrence, tumor resection, radiotherapy, or systemic chemotherapy was selected. As to chemotherapy, the patients received 5-fluorouracil (5-FU)-based chemotherapy as adjuvant and/or neo-adjuvant chemotherapy before 2003. Since 2004, the patients received infusional 5-FU/L-leucovorin with oxaliplatin (FOLFOX), and/or infusional 5-FU/L-leucovorin with irinotecan (FOLFIRI). Since 2007, patients have received FOLFOX and/or FOLFIRI with molecular-targeting drug. This retrospective study was approved by the Ethics Committee of Jikei University School of Medicine (#21-121).

Statistical analysis. Data were expressed as the mean±standard deviation (SD). Univariate analysis was performed using the non-paired Student's *t*-test and the Chi-square test. Analysis of overall survival was performed using the log-rank test. Factors that significantly influenced overall survival were then used in the Cox proportional regression model for multivariate analysis. All *p*-values were considered statistically significant when the associated probability was less than 0.05.

Results

Patients' characteristics. Patients' characteristics are outlined in Table I. For the study population, the mean age was 64.1 years, with a range from 39 to 85 years. Forty-five patients were males, and twenty patients were females. Twelve out of 65 patients underwent combined resection of the primary tumor and CRLM. Thirteen patients had bilobular tumor distribution. Twenty-seven patients received RC transfusion, and 23 patients received FFP transfusion, respectively. The five-year survival rate after hepatic resection was 46.7% (Figure 1).

Postoperative complications. Postoperative complications are listed in Table II. Postoperative complications developed in 19 out of the 65 patients (29.2%).

Univariate and multivariate analyses of clinicopathological variables in relation to overall survival after elective hepatic

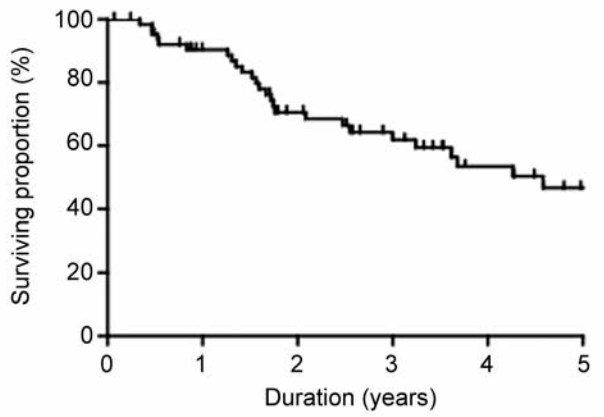

Figure 1. *The five-year survival rate after elective hepatic resection for colorectal liver metastases was 46.7% in this study.*

Table II. *Post-operative complications after hepatic resection for colorectal cancer liver metastases.*

Complication	Number of patients
Surgical site infection	7 (10.8%)
Bile leakage	5 (7.7%)
Pleural effusion	4 (6.2%)
Bowel obstruction	2 (3.1%)
Massive ascites	1 (1.5%)

resection for CRLM. Table III lists the relationship between the clinicopathological variables and overall survival after hepatic resection for CRLM. In univariate analysis, overall survival was worse in patients with bilobular tumor distribution (Figure 2A; p=0.0332), those with more than four lymph node metastases of the primary cancer (Figure 2B; p=0.0155), and those who received RC transfusion (Figure 2C; p=0.0205) or FFP transfusion (Figure 2D; p=0.0065). In multivariate analysis, bilobular tumor distribution (p=0.0012), more than four lymph node metastases of the primary cancer (p=0.0171), and FFP transfusion (p=0.0091) were independent risk factors for poorer overall survival.

Univariate analysis of clinicopathological variables in relation to perioperative FFP transfusion after hepatic resection for CRLM. Table IV lists the relationship between clinicopathological variables in patients with and without FFP transfusion. In univariate analysis, patients with FFP transfusion had significantly greater BMI (p=0.0113), intraoperative blood loss (p<0.0001), and unilobular tumor distribution (p=0.0196), than those in patients without FFP transfusion.

Table III. *Univariate and multivariate analyses of clinical variables in relation to overall survival after elective hepatic resection for colorectal cancer liver metastases.*

Factor	N	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	p-Value	Hazard ratio (95% CI)	p-Value
Age (years)					
≥65	33	1.307	0.4967		
<65	32	(0.6037 to 2.831)			
Gender					
Female	20	0.8708	0.7405		
Male	45	(0.3839 to 1.975)			
Body mass index (kg/m^2)					
≥25	9	1.277	0.6792		
<25	56	(0.4008 to 4.068)			
Procedure					
Anatomical	43	1.179	0.6839		
Partial	22	(0.5345 to 2.599)			
Duration of operation (min)					
≥300	37	1.258	0.5623		
<300	28	(0.5792 to 2.731)			
Blood loss (g)					
≥1,000	32	1.700	0.1778		
<1,000	33	(0.7857 to 3.678)			
Chemotherapy					
Yes	44	0.9267	0.8554		
No	21	(0.4084 to 2.103)			
Complications					
Present	19	1.158	0.7291		
Absent	46	(0.5054 to 2.652)			
Timing of liver metastasis					
Synchronous	28	0.7998	0.5720		
Metachronous	37	(0.3685 to 1.736)			
Tumor distribution					
Bilobular	13	3.173	0.0332	6.981	0.0012
Unilobular	52	(1.096 to 9.187)		(2.153 to 22.630)	
Lymph node metastases					
≥4	13	3.944	0.0155	3.029	0.0171
<4	52	(1.298 to 11.98)		(1.218 to 7.534)	
Primary cancer					
Colon	40	0.6855	0.3441		
Rectum	25	(0.3135 to 1.499)			
CEA (ng/ml)					
≥20	32	1.285	0.5244		
<20	33	(0.5937 to 2.781)			
RC transfusion					
Yes	27	2.539	0.0205	1.860	0.2362
No	38	(1.154 to 5.584)		(0.6660 to 5.190)	
FFP transfusion					
Yes	23	3.130	0.0065	4.935	0.0091
No	42	(1.375 to 7.126)		(1.486 to 16.391)	

CEA, Carcinoembryonic antigen; RC, red cell concentrate; FFP, fresh-frozen plasma; CI, confidence interval.

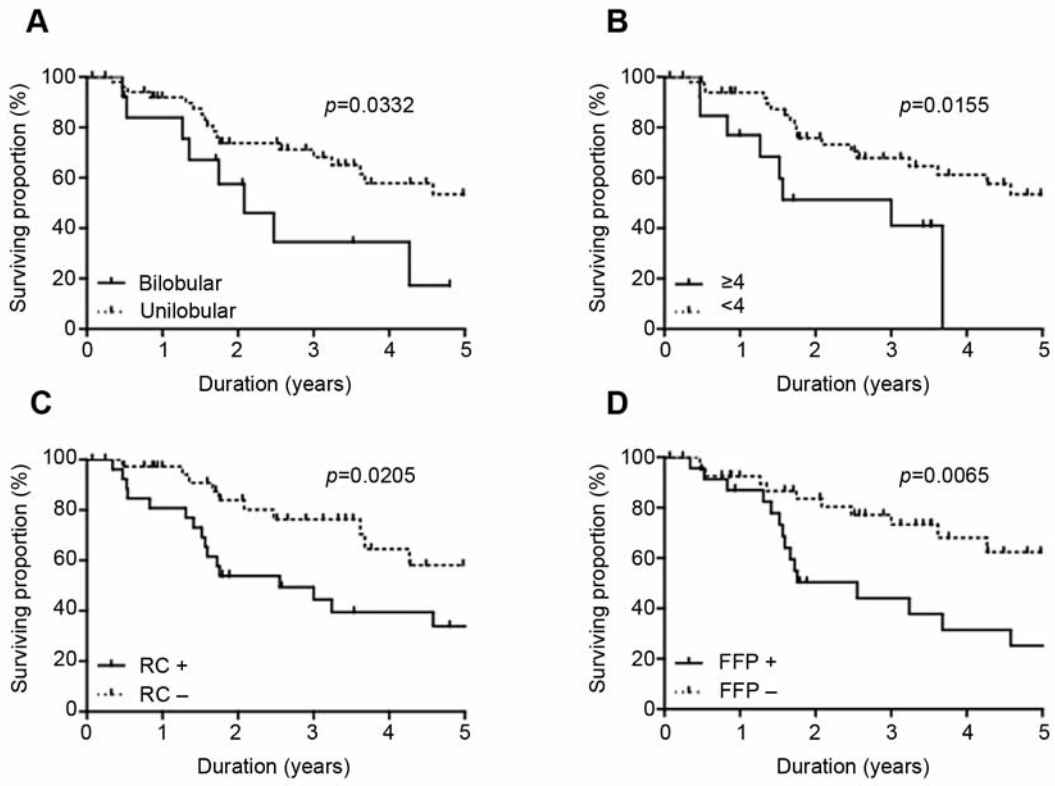

Figure 2. *Overall survival was worse in patients with bilobular tumor distribution (A; p=0.0332), those with more than four lymph node metastases of the primary cancer (B; p=0.0155), and in those who received RC transfusion (C; p=0.0205), and FFP transfusion (D; p=0.0065) in univariate analysis.*

Discussion

Because of the importance of CRLM on the prognosis of patients with colorectal cancer, their management is a common and important clinical problem. With increasing use of hepatic resection for CRLM, prognosis of patients with such a problem has significantly improved (42). Moreover, recent development of chemotherapeutic agents, such as oxaliplatin, bevacizumab, and cetuximab, brought further improvement in prognosis (43-45). On the other hand, these chemotherapeutic agents make liver tissue fragile and worsen liver function. Therefore, hepatic resection for CRLM is still associated with risks of excessive bleeding and postoperative liver failure. In the present study, perioperative blood transfusion, especially FFP transfusion, was significantly associated with reduced overall survival after elective and curative hepatic resection for CRLM. The result of our study seems to strengthen the negative impact of FFP transfusion on the prognosis of patients with CRLM. Concerning the mechanisms of immunosuppressive effects of blood transfusion, especially in FFP transfusion, soluble human leukocyte antigen (HLA) class I molecules and soluble fibroblast-associated surface (FAS)-ligand released by leukocytes present in the serum of blood products inhibit the activity of natural killer (NK) cells and cytotoxic T-cells, which are known to reduce immune capacity and therefore may predispose transfused patients to postoperative infections (16, 46-51). The absolute count of peripheral blood lymphocytes in the early post-operative period was significantly lower in patients who underwent intra-operative blood transfusion compared to that in those who did not (22). We have previously reported on the negative impact of FFP transfusion regarding infectious complications after elective hepatic resection for hepatocellular carcinoma (38) and CRLM (39). These reports suggest that plasma-rich blood products, such as FFP and PC, may lead to greater immunosuppressive effects by perioperative blood transfusion in patients during elective hepatic resection for CRLM.

Conclusion

Inspite of recent improvements in the outcome of elective hepatic resection, some complex surgical procedures still require blood transfusion, as compared to other types of surgery. In order to improve prognosis after the resection of malignancies, it is important not only to minimize blood transfusion but also for the mechanism of immunosuppression by blood transfusion to be further investigated.

Table IV. *Univariate analysis of clinical variables in relation to perioperative fresh-frozen plasma (FFP) transfusion after hepatic resection for colorectal cancer liver metastases.*

Factor	FFP transfusion		*p*-Value (univariate)
	Yes (n=23)	No (n=42)	
Age (years)	62.1±11.2*	65.2±10.8	0.2335
Gender (male:female)	16:7	29:13	0.9655
Body mass índex (kg/m^2)	23.3±2.6	21.7±2.3	0.0113
Procedure (anatomical:partial)	18:5	25:17	0.1269
Duration of operation (min)	345.1±118.8	330.7±136.4	0.6717
Blood loss (g)	2,014.8±1,273.4	758.2±556.8	<0.0001
Synchronous:metachronous	10:13	18:24	0.9614
Bilobular:unilobular	1:22	12:30	0.0196
Number of lymph node metastases	1.8±2.3	1.8±2.1	0.9763
Primary cancer (colon:rectum)	17:6	23:19	0.1291
CEA (ng/ml)	238.6±434.2	161.8±448.3	0.5070

CEA, Carcinoembryonic antigen; *mean±SD.

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