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Impact of Intraoperative Blood Loss and Blood Transfusion on the Prognosis of Colorectal Liver Metastasis Following Curative Resection

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Abstract. *Background/Aim: The identification of risk factors for recurrence after resection of colorectal liver metastasis is necessary in order to establish a more effective treatment strategy. In addition to well-known prognostic factors, such as the tumor diameter and number of metastatic tumors, a large amount of intraoperative blood loss (IBL) and blood transfusion have recently been reported to be associated with shorter long-term survival. The aim of this study was to assess the impact of IBL and blood transfusion on the prognosis of colorectal liver metastasis after curative resection. Patients and Methods: A total of 104 patients who underwent R0 resection for colorectal liver metastasis were enrolled in this study. Results: The high-IBL (>300 ml) group had significantly shorter relapse-free survival after hepatic resection in comparison to the low-IBL (≤300 ml) group (p=0.0025). Patients with blood transfusion had significantly shorter relapse-free survival after hepatic resection in comparison to patients without blood transfusion (p=0.0026). Conclusion: A large amount of IBL and blood transfusion may have a negative impact on long-term survival in patients who undergo hepatic resection for colorectal liver metastasis.*

Regarding colorectal cancer, the most common target organ of synchronous distant metastasis and recurrence after curative surgery is the liver (1-3). Hepatic resection is the only potentially curative treatment and offers an opportunity to achieve a long-term survival benefit (4-7). However, the recurrence rate is very high, at 70-80% even after potentially curative surgery (8-10). Therefore, the identification of risk factors for recurrence after resection of colorectal liver metastasis is necessary in order to establish a more effective treatment strategy. In addition to well-known prognostic factors, such as the tumor diameter, the number of metastatic tumors and N-stage of the primary tumor (11, 12), host factors, such as preoperative and postoperative inflammatory markers and Clinical Frailty Scale have recently been reported to be useful prognostic markers in patients with colorectal liver metastasis (13-15). Furthermore, a large amount of intraoperative blood loss (IBL) and blood transfusion have been reported to be associated with shorter long-term survival in patients with colorectal liver metastasis as well as other malignancies (16-21).

Previous studies on IBL and blood transfusion have often focused on short-term outcomes, such as morbidity and mortality rather than long-term survival outcomes (22-24). Due to the advances in surgical techniques, the development of surgical devices and improvement of perioperative management, the mortality rate after hepatic resection has decreased remarkably (25). Under such circumstances, the impact of the amount of IBL and blood transfusion on long-term survival is unclear. The aim of this study was to assess the impact of IBL and blood transfusion on the prognosis of colorectal liver metastasis after curative resection.

Patients and Methods

Patients. A total of 104 patients who underwent R0 resection for colorectal liver metastasis at Osaka City University Hospital between January 2001 and December 2017 were enrolled in this

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Key Words: Colorectal liver metastasis, prognosis, blood transfusion, intraoperative blood loss.

study. R0 resection was defined as no microscopic evidence of the tumor at or within 1 mm of the margin. Two cases of simultaneous multiple primary cancer were excluded from this study.

This retrospective study was approved by the Ethics Committee of Osaka City University (approval number: 4182) and was conducted in accordance with the Declaration of Helsinki. All patients provided their written informed consent.

Methods. The appropriate cut-off value of the amount of IBL was determined by a receiver operating characteristic (ROC) curve analysis. The patients were then classified into the low-IBL and high-IBL groups, and the relationship between the amount of IBL/blood transfusion and relapse-free survival was assessed.

Statistical analyses. Relapse-free survival was defined as the interval between the date of hepatic resection and the date of the diagnosis of the first recurrence, death from any cause or last follow-up examination. The significance of differences in the amount of IBL/blood transfusion and clinicopathological factors were analyzed using a chi-squared test, Fisher's exact test, and Mann-Whitney *U*-test. Survival curves were estimated using the Kaplan–Meier method, and differences in survival curves were assessed with the log-rank test. A multivariate Cox proportional hazards model was used to evaluate the prognostic factors associated with the survival. Factors with a *p*-value of <0.1 in a univariate analysis were included in the multivariate analysis. *p*-Values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the SPSS software package for Windows (SPSS, Chicago, IL, USA).

Results

Patient characteristics. The patient characteristics are shown in Table I. The median age of the 104 patients (male, n=55; female, n=49) was 65.5 years (range=22-87 years). The median amount of IBL was 335 ml (range=3-2,225 ml). Nineteen patients (18.3%) received blood transfusion. The median length of follow-up was 55.8 months (range=0.4-170.3 months). Seventy-two patients (69.2%) relapsed during the follow-up period. There was no perioperative death within 30 days after surgery.

Determination of the optimal IBL cut-off value. We used the amount of IBL, which was a continuous variable, as the test variable and recurrence as the state variable. When we investigated the cut-off value for IBL using the ROC curve analysis, we found that the most appropriate cut-off value was 302 (sensitivity: 61.6%; specificity: 67.7%) (Figure 1). We therefore set 300 as the cut-off value and classified patients into the high-IBL (n=55) and low-IBL (n=49) groups.

Risk factors associated with blood transfusion. The performance of blood transfusion was significantly associated with a large amount of IBL and tended to be associated with larger metastatic tumors (Table II).

Table I. *Patient characteristics*.

Age (years)	
Median (range)	65.5 (22-87)
Gender, n	
Male	55
Female	49
Detection of liver metastasis, n	
Synchronous	52
Metachronous	52
Size of largest metastatic liver tumor (cm)	
Median (range)	2.85 (0.4-13.0)
Number of metastatic liver tumors, n	
1	54
≥2	50
Histological type of primary tumor, n	
Well/moderately differentiated	98
Poorly differentiated/Mucinous	3
Unknown	3
Depth of primary tumor, n	
T1-3	67
T4	35
Unknown	2
Lymph node metastasis of primary tumor, n	
Negative	41
Positive	61
Unknown	2
Serum CEA level (ng/ml), n	
≤5.0	23
>5.0	80
Unknown	1
Amount of bleeding (ml)	
Median (range)	335.0 (3-2,225)

CEA: Carcinoembryonic antigen.

Risk factors associated with a larger amount of IBL. A larger amount of IBL was significantly associated with the performance of blood transfusion, the number of metastatic tumors and serum carcinoembryonic antigen (CEA) levels, and tended to be associated with larger metastatic tumors (Table II).

Survival analyses according to IBL and blood transfusion. The high-IBL group had significantly shorter relapse-free survival after hepatic resection in comparison to the low-IBL group (p=0.0025) (Figure 2). Patients with blood transfusion had significantly shorter relapse-free survival after hepatic resection in comparison to patients without blood transfusion (p=0.0026) (Figure 3).

Prognostic factors for relapse-free survival identified by univariate and multivariate analyses. Table III presents the prognostic factors for relapse-free survival. According to the univariate analyses, relapse-free survival was significantly associated with the number of metastatic tumors, the amount of IBL and blood transfusion, and tended to be associated

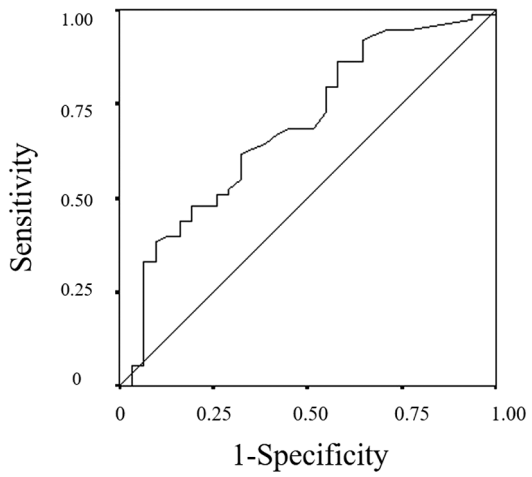

Figure 1. *A receiver operating characteristic curve analysis of intraoperative blood loss. Area under the curve=0.688; 95% confidence interval=0.575-0.800; p=0.003.*

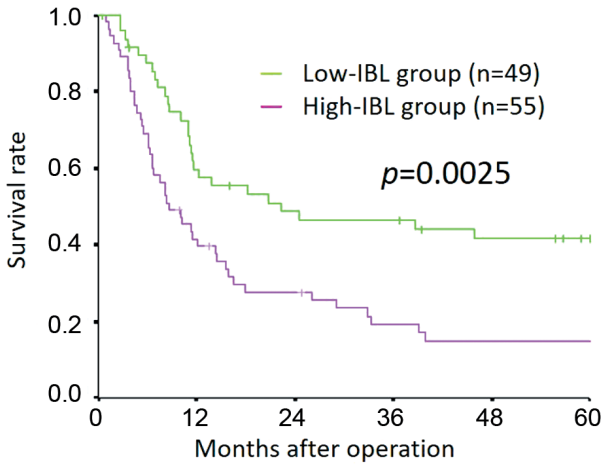

Figure 2. *Kaplan–Meier survival curve for relapse-free survival according to the amount of intraoperative blood loss (IBL). A large amount of IBL was associated with shorter relapse-free survival (p=0.0025).*

with the N-stage of the primary tumor and the serum CEA levels. According to the multivariate analyses, relapse-free survival was significantly associated with the number of metastatic tumors and the N-stage of primary tumor, and tended to be associated with the amount of IBL.

Discussion

In this study, a large amount of IBL and blood transfusion were shown to be associated with worse relapse-free survival after the resection of colorectal liver metastasis, although these two factors were not found to be independent prognostic factors for relapse-free survival in the multivariate analysis.

Since it was reported in 1982 that blood transfusion worsens the long-term survival of patients undergoing surgery for colorectal cancer (26), the relationship between blood transfusion and worse long-term survival has been reported in various malignancies (27-29), and this negative impact of blood transfusion on long-term survival has been reported to be dose dependent (30). The mechanism by which blood transfusion worsens long-term survival is thought to be as follows. Blood transfusion has been reported to cause immunosuppression through decreased activity of cytotoxic T cells, natural killer cells and monocytes, a decrease in the absolute number of natural killer cells, the release of immunosuppressive prostaglandins, the inhibition of IL-2 production and the activation of suppressor T cells, resulting in an increased risk of recurrence (31).

An increasing amount of IBL, as well as blood transfusion, has been reported to have a negative impact on long-term

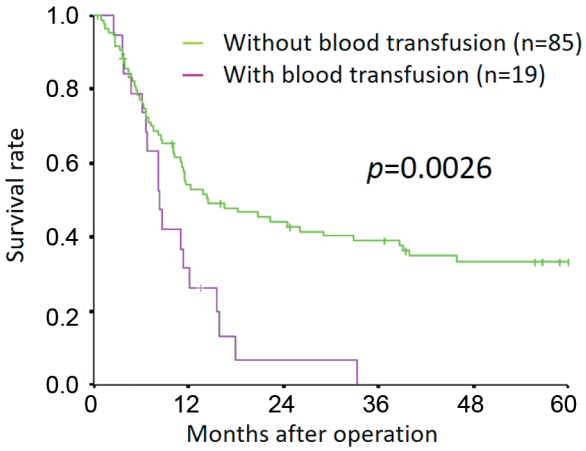

Figure 3. *Kaplan–Meier survival curve for relapse-free survival according to blood transfusion. Blood transfusion was associated with shorter relapse-free survival (p=0.0026).*

survival (18, 19), and the detrimental effect of IBL on long-term survival has been reported to be dose dependent (18, 19). The hypothetical mechanism underlying the detrimental effect of IBL on long-term survival is as follows. A large amount of IBL may promote intraoperative tumor spillage and hematogenous spread during the operation (32, 33). Furthermore, a large amount of IBL promotes systemic inflammation and induces a cytokine milieu, resulting in the suppression of antitumor immunity (34).

Table II. *Correlation between intraoperative blood loss/blood transfusion and clinicopathological factors.*

	Intraoperative blood loss			Blood transfusion		
Factors	Low (n=49)	High (n=55)	*p*-Value	Negative (n=85)	Positive (n=19)	*p*-Value
Gender, n						
Male	24	31		48	7	
Female	25	24	0.555	37	12	0.136
Age (years)						
Median (range)	68 (22-87)	64 (32-83)	0.553	64 (22-87)	74 (49-83)	0.104
Detection of liver metastasis, n						
Synchronous	25	27		42	10	
Metachronous	24	28	>0.999	43	9	>0.999
Size of largest metastatic liver tumor (cm)						
Median (range)	2.5 (0.4-9.0)	3.1 (0.7-13.0)	0.072	2.5 (0.4-9.0)	4.2 (1.8-13.0)	0.070
Number of metastatic liver tumors, n						
1	31	23		45	9	
≥2	18	32	0.033	40	10	0.801
Histological type of primary tumor, n						
Well/moderately differentiated	48	50		82	16	
Poorly differentiated/Mucinous	1	2	>0.999	2	1	0.428
Unknown	0	3		1	2	
Depth of primary tumor, n						
T1-3	36	31		57	10	
T4	13	22	0.145	27	8	0.413
Unknown	0	2		1	1	
Lymph node metastasis of primary tumor, n						
Negative	19	22		34	7	
Positive	30	31	0.841	50	11	>0.999
Unknown	0	2		1	1	
CEA level before hepatic resection (ng/ml), n						
≤5	17	6		20	3	
>5	32	48	0.005	64	16	0.554
Unknown	0	1		1	0	
Blood transfusion, n						
Negative	48	37				
Positive	1	18	<0.001			

CEA: Carcinoembryonic antigen.

The relationship between the amount of IBL/blood transfusion and long-term survival is complicated, as these two factors are associated with various confounding factors. First, a few decades ago, it was reported that a large amount of IBL and blood transfusion may be associated with worse survival outcomes, because patients with high-IBL and those who received blood transfusion were more likely to die in the immediate postoperative period (22-24). However, due to advances in surgical techniques and perioperative care, the mortality rate has dramatically decreased in recent years (25). As there were no surgery-related deaths in this study, the relationship between a large amount of IBL/blood transfusion and a poor prognosis obtained in this study can be considered as oncological outcome. Second, hepatic resection for large tumors and multiple tumors often requires a large excision volume, resulting in increased IBL and frequent blood transfusion. Therefore, the proportion of advanced cases may be high in cases with a large amount of IBL or blood transfusion, and the degree of cancer progression may be a confounding factor. However, given that several studies have reported that a large amount of IBL and blood transfusion are independent prognostic factors for long-term survival (18, 19, 35, 36), it is possible that a large amount of IBL and blood transfusion themselves are associated with shorter long-term survival.

One of the reasons that makes it difficult to interpret the results of the analysis on the prognostic impact of IBL and blood transfusion is that the amount of IBL and blood transfusion are closely related to each other. In contrast to primary tumors, anemia is rarely caused by bleeding from metastatic liver tumors. Therefore, the relationship between a large amount of IBL and blood transfusion is more relevant in metastatic liver tumors than in primary tumors. In this study, a large amount of IBL and blood transfusion were significantly

Table III. *The correlation between the relapse-free survival and various clinicopathological factors.*

	Univariate analysis			Multivariate analysis		
	Hazard Ratio	95%CI	*p*-Value	Hazard Ratio	95%CI	*p*-Value
Age (>65 *vs.* ≤65 years)	0.863	0.545-1.368	0.531			
Gender (Female *vs.* Male)	1.191	0.751-1.886	0.458			
Detection of liver metastasis (Synchronous *vs.* Metachronous)	1.122	0.708-1.777	0.624			
Histological type of primary tumor (Poorly differentiated, Mucinous vs. Well-/Moderately differentiated)	1.000	0.245-4.085	>0.999			
Depth of primary tumor (T4 *vs.* T1-3)	0.981	0.605-1.591	0.939			
Lymph node metastasis of primary tumor (Positive *vs.* Negative)	1.537	0.947-2.496	0.082	1.679	1.028-2.742	0.039
Size of largest metastatic liver tumor (>5 *vs.* ≤5 cm)	1.131	0.609-2.103	0.696			
Number of metastatic liver tumors (≥2 *vs.* 1)	1.809	1.139-2.872	0.012	1.706	1.039-2.801	0.035
Serum CEA level (>5 *vs.* ≤5 ng/ml)	1.715	0.939-3.131	0.079	1.227	0.621-2.428	0.556
Amount of intraoperative blood loss (>300 *vs.* ≤300 ml)	2.054	1.276-3.305	0.003	1.579	0.917-2.717	0.099
Blood transfusion (Positive *vs.* Negative)	2.282	1.314-3.964	0.003	1.615	0.882-2.957	0.120

CI: Confidence interval; CEA: carcinoembryonic antigen.

associated with long-term survival in the univariate analyses, but these two factors were not found to be independent prognostic factors for long-term survival in the multivariate analysis. These results may have been influenced by the strong correlation between a large amount of IBL and blood transfusion. It is difficult to assess the separate effects of IBL and blood transfusion on long-term survival, and it is likely that both have a negative impact on long-term survival.

The present study has some limitations. First, the current study was a retrospective study with a relatively small cohort, and was conducted at a single center. Second, there were many differences in patient background factors, such as the tumor diameter and the number of metastatic tumors. Third, we only assessed relapse-free survival, because the patient data were collected over a period of 17 years during which there were major changes in chemotherapy after recurrence.

Due to advances in surgical techniques and the development of surgical devices, the average amount of IBL has decreased. However, hepatectomy sometimes causes massive bleeding. Surgeons should make efforts to minimize the amount of IBL and avoid blood transfusion, which may further improve treatment outcomes of patients with colorectal liver metastasis.

Conclusion

In conclusion, a large amount of IBL and blood transfusion may have negative impact on long-term survival in patients who undergo hepatic resection for colorectal liver metastasis; however, the separate effects of these two factors are difficult to be evaluated due to strong correlation between them and the presence of various confounding factors. Surgeons should make efforts to minimize the amount of IBL and avoid blood transfusion to improve the patient's prognosis.

Conflicts of Interest

The Authors declare no conflicts of interest in association with the present study.

Authors' Contributions

MS designed the study, performed the statistical analysis and drafted the manuscript. KK, SK, WE, YO, KM, KH and MO designed the study and critically reviewed the manuscript. All Authors read and approved the final manuscript.

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