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The Impact of Intraoperative Blood Loss on the Survival After Laparoscopic Surgery for Colorectal Cancer

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Abstract. *Background/Aim: Blood transfusion and a large amount of intraoperative blood loss (IBL) have been reported to have a negative impact on long-term survival via immunosuppression. In recent years, thanks to the spread of laparoscopic surgery and the development of surgical devices, the average amount of IBL has decreased, as has the need for perioperative blood transfusion. Under such conditions, the prognostic significance of the amount of IBL is unclear. The aim of this study was to assess the impact of the amount of IBL on long-term survival. Patients and Methods: A total of 277 patients who underwent laparoscopic surgery for stage II/III colorectal cancer were enrolled. Results: The median amount of IBL was 30 ml, and 16 patients received blood transfusion. The overall survival rates were significantly better in the low-IBL (≤100 ml) group than in the high-IBL (>100 ml) group regardless of the blood transfusion. As the amount of IBL increased, the decline rate of the peripheral lymphocyte count increased. Conclusion: A large amount of IBL was associated with poor long-term survival, regardless of blood transfusion, in patients with colorectal cancer.*

R0 resection is the only potentially curative treatment for colorectal cancer. However, recurrence is a significant concern, even after R0 resection. Tumor depth and lymph node metastasis, which are well-known prognostic factors, are routinely used for stratification of risk of recurrence in clinical practice. Recently, in addition to these factors associated with the tumor, factors associated with the host, such as the neutrophil-to-lymphocyte ratio and CONUT score (1, 2), have received attention. Furthermore, blood transfusion and a large amount of intraoperative blood loss (IBL) have been reported to have a negative impact on long-term survival *via* immunosuppression in patients with various malignancies (3-9).

In recent years, thanks to the spread of laparoscopic surgery and the development of surgical devices such as electrothermal bipolar-activated devices or ultrasonic systems, the average amount of IBL has decreased, as has the need for perioperative blood transfusion. Under these conditions, the prognostic significance of the amount of IBL is unclear. Furthermore, few studies have specifically investigated the mechanism by which immunosuppression caused by IBL worsens the prognosis.

The present study assessed the impact of the amount of IBL on the long-term survival and on the postoperative immune status of patients who underwent curative operation for colorectal cancer.

Patients and Methods

A total of 277 patients who underwent laparoscopic surgery for stage II/III colorectal cancer at Osaka City University Hospital between January 2012 and December 2016 were enrolled in this study. All patients enrolled in this study underwent curative resection. Patients who received preoperative therapy, such as neoadjuvant chemoradiotherapy, underwent emergency surgery for perforation or obstruction, and patients with ulcerative colitis or familial adenomatous polyposis 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.

The relationship between the amount of IBL and the overall survival rate were assessed. An appropriate cut-off value for the amount of IBL was determined based on a receiver operating

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characteristic (ROC) curve analysis, and the patients were then classified into the low- (≤100 ml) and high-IBL (>100 ml) groups based on the cut-off value. Furthermore, the relationships between IBL and the clinicopathological factors were assessed in order to identify the factors that were associated with an increasing amount of IBL. The preoperative absolute peripheral lymphocyte count-to-postoperative absolute lymphocyte count ratio (rate of decline in the peripheral lymphocyte count) was calculated by dividing the absolute peripheral lymphocyte count on postoperative day 7 by that within two weeks before the operation.

All statistical analyses were performed using the SPSS software package for Windows (SPSS, Chicago, IL, USA). The significance of differences in IBL and the clinicopathological factors were analyzed using a chi-squared test and Fisher's exact test. Survival curves were estimated using the Kaplan–Meier method, and the differences in the survival curves were assessed with a log-rank test. A multivariate Cox proportional hazard model was used to evaluate the prognostic factors associated with the survival. Factors with a p-value of <0.1 on the univariate analysis were included in the multivariate analysis. p-values of <0.05 were considered to indicate statistical significance.

Results

Patient characteristics. The patient characteristics are shown in Table I. The median amount of IBL was 30 (range=5-2,120) ml. Sixteen patients (5.8%) received blood transfusion. The median duration of follow-up was 48.0 months. Fifty-four patients relapsed, and 54 died during the follow-up period. Among the patients enrolled in this study, no patients died within 30 days after surgery.

Classifications according to the amount of IBL. We used the amount of IBL, which was a continuous variable, as the test variable and the five-year survival 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 107 (sensitivity: 35.2%; specificity: 79.4%) (Figure 1). We therefore set 100 as the cut-off value and classified patients into the high-IBL group (n=66) or the low-IBL group (n=211).

Correlations between IBL and clinicopathological factors. The correlations between IBL and the clinicopathological factors are shown in Table II. The amount of IBL was significantly associated with depth, lymphatic involvement, and venous involvement (Table II).

Survival analyses according to IBL and blood transfusion. The overall survival rates were significantly better in the low-IBL group than in the high-IBL group (p=0.0293) (Figure 2). The overall survival rates tended to be worse in patients who received blood transfusion than in those who did not receive blood transfusion (p=0.0880) (Figure 3).

Subgroup analyses limited to the patients without blood transfusion. The overall survival rates were significantly better in the low-IBL group than in the high-IBL group (p=0.0240) (Figure 4). The correlations between the overall survival and various clinicopathological factors are shown in Table III. According to the results of the univariate analyses, the overall survival was significantly associated with the amount of IBL and tumor depth and tended to be associated with age and histological type. The multivariate analyses indicated that the overall survival was significantly

Table I. *Patient characteristics*.

Age (years)	
Median (range)	71 (21-92)
Gender, n	
Male	162
Female	115
Location of the tumor, n	
Right side	79
Left side	198
Histological type, n	
Well-/moderately differentiated	259
Poorly differentiated	8
Mucinous	7
Signet	2
Unknown	1
Tumor diameter, n	
<5 cm	164
≥5 cm	113
Depth of tumor, n	
T1-3	219
T4	58
Lymphatic involvement, n	
Negative	118
Positive	155
Unknown	4
Venous involvement, n	
Negative	172
Positive	102
Unknown	3
Lymph node metastasis, n	
Negative	143
Positive	134
Serum CEA level, n	
≤5.0 ng/ml	183
>5.0 ng/ml	92
Unknown	2
Amount of intraoperative blood loss, ml	
Median (range)	30 (5-2,120)
Blood transfusion, n	
Negative	261
Positive	16
Preoperative peripheral absolute lymphocyte count, /μl	
Median (range)	1549 (317-3,478)
Postoperative peripheral absolute lymphocyte count, /μl	
Median (range)	1292 (253-3,456)

CEA: Carcinoembryonic antigen.

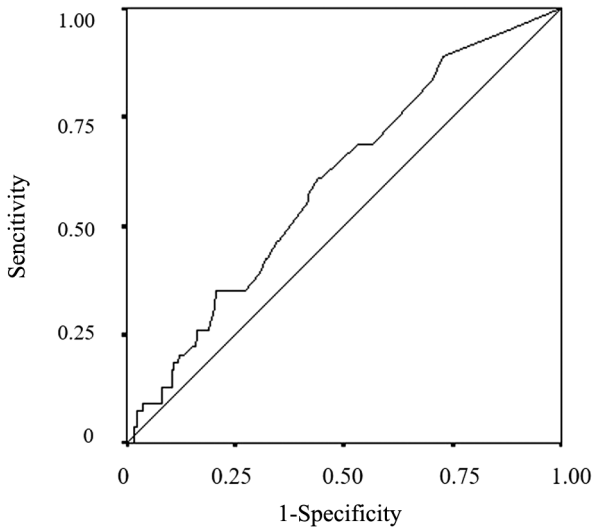

Figure 1. *A receiver operating characteristic curve analysis of the intraoperative blood loss. Area under the curve=0.600; 95% Confidence Interval=0.519-0.681; p=0.022.*

associated with age and tended to be associated with the amount of IBL and tumor depth.

Comparison of the rate of decline in the peripheral lymphocyte count according to the amount of IBL. The decline rate of peripheral lymphocyte count was significantly higher in the high-IBL group than in the low-IBL group (Figure 5).

Discussion

In previous reports, perioperative blood transfusion was reported to have a negative impact on the long-term survival *via* immunosuppression in various malignancies (7-9). However, many points concerning the impact of an increased amount of IBL on the prognosis have been unclear. As a large amount of IBL increases the need for blood transfusion, the relationship between a large amount of IBL and a poor prognosis may be influenced by blood transfusion. However, in the present study, an increased amount of IBL was associated with a poor prognosis even in patients who did not receive blood transfusion. Therefore, an increased amount of IBL was revealed to be associated with a poor prognosis, regardless of blood transfusion.

Several mechanisms could be responsible for the association between the amount of IBL and worse prognosis. First, an increasing amount of IBL may cause immunosuppression, resulting in a poor prognosis. The present study revealed that as the amount of IBL increased, the rate of decrease in the peripheral lymphocyte count increased. Although the degree of the effect of peripheral lymphocyte depletion on the immune status is unclear, considering the existence of reports on the correlation between the number of peripheral lymphocytes and the prognosis after potentially curative operation (10-13), it is possible that increasing the IBL may worsen the prognosis *via* immunosuppression. Second, excessive blood loss may promote intraoperative tumor spillage and hematogenous spread during the operation (14, 15). Third, the amount of IBL indirectly represents the degree of cancer progression, as can be seen from the correlation between the amount of IBL and the tumor depth. However, the amount of IBL itself is considered to be an important prognostic factor, since the

Table II. *Correlation between intraoperative blood loss and clinicopathological factors in patients without blood transfusion.*

	Low-IBL group (n=211)	High-IBL group (n=66)	*p*-Value
Age, n			
<70 years old	95	34	
≥70 years old	116	32	0.397
Gender, n			
Male	123	39	
Female	88	27	>0.999
Location of the tumor, n			
Right side	60	19	
Left side	151	47	>0.999
Histological type, n			
Well-/moderately differentiated	198	61	
Poorly differentiated, Mucinous, Signet	12	5	0.565
Unknown	1	0	
Tumor diameter, n			
≤5 cm	122	42	
>5 cm	89	24	0.474
Depth of tumor, n			
T1-3	175	44	
T4	36	22	0.009
Lymphatic involvement			
Negative	99	19	
Positive	110	45	0.014
Unknown	2	2	
Venous involvement			
Negative	139	33	
Positive	71	31	
Unknown	1	2	0.039
Lymph node metastasis, n			
Negative	112	31	
Positive	99	35	0.401
Serum CEA level, n			
≤5.0 ng/ml	140	43	
>5.0 ng/ml	69	23	0.767
Unknown	2	0	
Transfusion, n			
Negative	205	56	
Positive	6	10	0.001

CEA: Carcinoembryonic antigen.

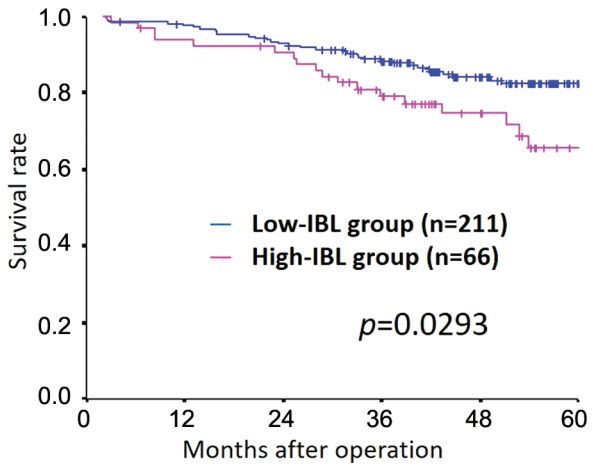

Figure 2. *Kaplan–Meier survival curves for the overall survival according to the intraoperative blood loss (IBL). The low-IBL group had a significantly better overall survival rate than the high-IBL group (p=0.0293).*

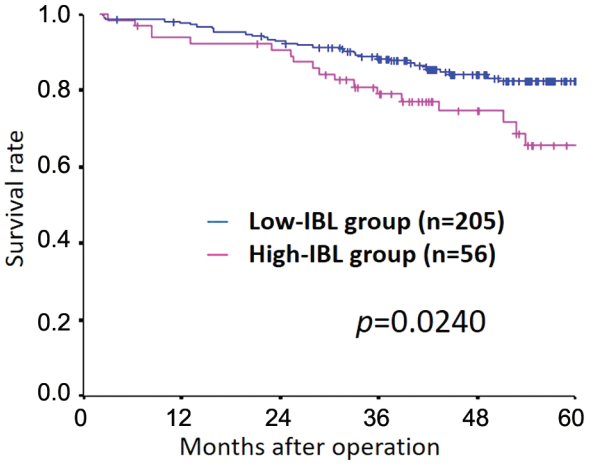

Figure 4. *Kaplan–Meier survival curves for the overall survival according to the intraoperative blood loss (IBL) in patients without blood transfusion. The low-IBL group had a significantly better overall survival rate than the high-IBL group (p=0.0240).*

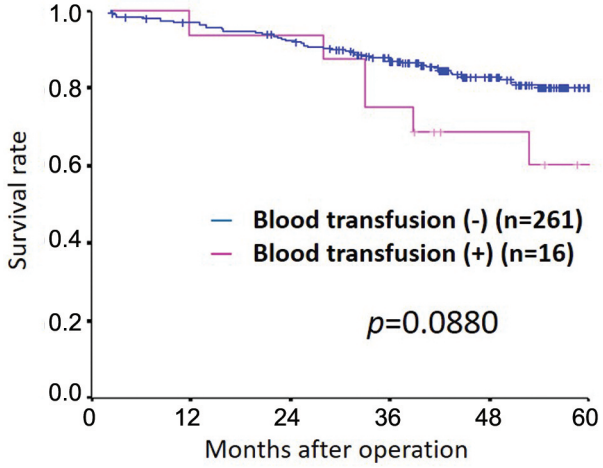

Figure 3. *Kaplan–Meier survival curves for the overall survival according to the blood transfusion. The overall survival rates tended to be worse in patients who received blood transfusion than in those who did not receive blood transfusion (p=0.0880).*

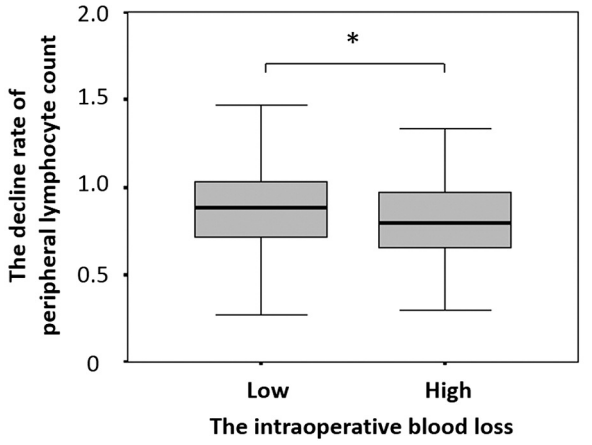

Figure 5. *A comparison of the rate of decline in the peripheral lymphocyte count according to the amount of intraoperative blood loss (IBL). The rate of decline in the peripheral lymphocyte count was significantly higher in the high-IBL group than in the low-IBL group. *p=0.038.*

amount of IBL tended to correlate with the survival time, even in the multivariate analysis including the tumor depth as a covariate. Fourth, an increased amount of IBL leads to excessive surgical stress, which promotes the production of inflammatory cytokines (16). Inflammatory cytokines provide a favorable environment for the proliferation of micrometastasis, resulting in a poor prognosis (17-20). Fifth, increasing the amount of IBL worsens the prognosis *via* postoperative complications. Increased IBL has been reported to be associated with increased postoperative complications (21, 22). Postoperative infectious complications as well as surgical stress are associated with worse survival outcomes due to the increased production of inflammatory cytokines (23-25).

The present study has several limitations. First, this was a retrospective study with a small cohort performed in a single

Table III. *The correlation between the overall survival and various clinicopathological factors in patients without blood transfusion.*

	Univariate analysis			Multivariate analysis		
	Hazard Ratio	95%CI	*p*-Value	Hazard Ratio	95%CI	*p*-Value
Age (≥70 *vs.* <70 years old)	1.777	0.971-3.254	0.062	1.868	1.010-3.455	0.046
Gender (Male *vs.* Female)	0.989	0.553-1.766	0.969			
Location of the tumor (Right side *vs.* Left side)	0.618	0.340-1.126	0.116			
Tumor diameter (>5 *vs.* ≤5 cm)	1.115	0.623-1.994	0.715			
Tumor depth (T4 *vs.* T1-3)	2.328	1.287-4.209	0.005	1.821	0.974-3.404	0.060
Histological type (Poorly differentiated, Mucinous, Signet *vs.* Well-/Moderately differentiated)	2.275	0.950-5.444	0.065	1.914	0.760-4.820	0.168
Lymphatic involvement (Positive *vs.* Negative)	1.647	0.889-3.051	0.112			
Venous involvement (Positive *vs.* Negative)	1.355	0.766-2.398	0.297			
Lymph node metastasis (Positive *vs.* Negative)	1.229	0.695-2.173	0.478			
Serum CEA level (>5 *vs.* ≤5 ng/ml)	1.029	0.559-1.896	0.927			
Amount of intraoperative blood loss (>100 *vs.* ≤100 ml)	1.992	1.083-3.664	0.027	1.778	0.941-3.361	0.076

CI: Confidence interval; CEA: carcinoembryonic antigen.

center. Second, some of the proposed mechanisms by which increasing IBL worsens the prognosis remain a matter of debate. Specifically, the theory that excessive IBL may promote intraoperative tumor spillage and hematogenous spread during the operation is only speculation, and proof supporting this mechanism is lacking at present. Third, regarding immunosuppression, although this study revealed that the peripheral lymphocyte count decreases as the amount of IBL increases, other immunocompetent cells have not been evaluated.

In conclusion, it was revealed that a large amount of IBL is associated with a poor long-term survival outcome, regardless of blood transfusion, in patients with colorectal cancer. Preventing massive intraoperative bleeding may improve the prognosis after curative operation for colorectal cancer.

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. KM, SK, KH and MO designed the study and critically reviewed the manuscript. All Authors read and approved the final manuscript.

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