

Impact of Intraoperative Blood Loss on the Survival of Patients With Stage II/III Colorectal Cancer: A Multicenter Retrospective Study

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Abstract. *Background:* Resection of the primary lesion with radical lymph node dissection is the most promising treatment avenue for patients with cancer. On the other hand, these procedures often induce excessive intraoperative blood loss (IBL) and require perioperative blood transfusion. The influence of IBL on the long-term postoperative outcomes of patients with digestive cancer is controversial. We investigated the impact of IBL on survival and recurrence after curative surgery in patients with colorectal cancer (CRC) in a single study group. *Patients and Methods:* In total, 1,597 patients who underwent radical resection for CRC at three group hospitals between 2000 and 2019 were reviewed. Patients were classified into a group with high IBL (≥ 200 ml) or low IBL (< 200 ml). The risk factors for disease-free (DFS) and overall (OS) survival were analyzed. *Results:* A total of 489 and 1,108 patients were classified into the high and low IBL groups, respectively. The OS and DFS rates at 5 years after surgery were 89.3% and 63.4%, respectively, for the high IBL group and 96.9% and 77.8%

for the low IBL group; these differences were statistically significantly ($p < 0.001$). The multivariate analysis demonstrated that IBL was a significant independent risk factor for OS and DFS. *Conclusion:* The amount of IBL was associated with significant differences in the OS and DFS of patients with stage II/III CRC who received curative resection. The surgical procedure, surgical strategy, and perioperative care should be carefully planned to avoid causing IBL.

Colorectal cancer (CRC) remains the fourth cancer-specific cause of death worldwide and the second and third leading cause in males and females, with an estimated 1.09 million new cases and 551,200 deaths occurring in 2018 (1). Complete resection is essential to obtain a cure in cases of CRC. 5-Year relative survival of patients diagnosed with CRC was 90.1% for patients with localized stage, 69.2% for patients with regional spread, and 11.7% for patients with distant tumor spread. In particular, patients with stage II/III CRC often develop recurrence, even after complete curative resection. It is reported that approximately 21-42% of patients with stage II/III CRC develop recurrent disease, such as local recurrence or distant metastasis (2). Recently, adjuvant treatment was introduced for stage II/III CRC and has improved patient survival (3, 4). Consequently, it is important to determine prognostic factors for stage II/III CRC, as it would facilitate the selection of patients who can benefit from more aggressive treatment. In patients with CRC, Burrow and Tartter (5) were the first to report the risk associated with perioperative blood transfusion in 1982. Since then, some reports have documented the relationship between intraoperative blood loss (IBL) and a poor prognosis of patients with some types of cancer (6-11). However,

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research on the association between IBL and the long-term outcomes of patients with CRC remains limited.

The purpose of this multicenter retrospective study was to determine whether overall (OS) and disease-free (DFS) survival were affected by the degree of intraoperative blood loss in patients who underwent curative resection of stage II/III CRC.

Patients and Methods

Study design. The database of Yokohama City University (Department of Surgery) and three group facilities, which included data obtained between January 2000 and December 2019, was retrospectively reviewed. According to these records, a total of 2,205 patients with CRC underwent radical resection of primary lesions. Of these, we excluded cases with pathological stage I or IV, synchronous or multiple cancer, simultaneous operation of other organs, and non-curative resection. Finally, 1,597 patients who were diagnosed with pathological stage II/III, and who underwent curative resection were enrolled in this study.

All procedures performed in the study were in accordance with the ethical standards of the institutional research committee (Yokohama City University Institutional Review Board; approval no. 170700003) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Outcomes of interest. The primary outcome of this cohort study was 5-year disease-free survival (DFS). The secondary outcomes were 5-year OS and short-term outcomes, such as operative time and the incidence of postoperative complications. OS was defined as the period from the first resection of the primary lesion until death. DFS was defined as the period from the first resection of the primary lesion until recurrence or death. Operative time was defined as the time from skin incision for the first port to the completion of all surgical incisions. Postoperative complications were assessed by the Clavien-Dindo classification system (12). This study recorded grade 3-5 postoperative complications that occurred during hospitalization and those that occurred within 30 days after surgery.

Evaluations and statistical analyses. The optimal cut-off value of IBL was investigated by a receiver operating characteristic (ROC) curve analysis. The significance of the correlation between the IBL and clinicopathological parameters was determined using Fisher’s test or the chi-squared test. OS and DFS curves were determined using the Kaplan-Meier method and were compared by a log-rank test. OS and DFS were evaluated by univariate and multivariate analyses using a Cox proportional hazards model. *p*-Values of less than 0.05 were considered to indicate statistical significance. The survival data were derived from hospital records or from the city registry system. The SPSS software program (v26. J Win; SPSS, Chicago, IL, USA) was used for all statistical analyses.

Results

Patient characteristics and short-term outcomes. IBL of 200 ml exhibited the maximum sensitivity and specificity on the ROC plot and was set as the optimum cut-off value for classification (95% confidence interval=0.573-0.694; area

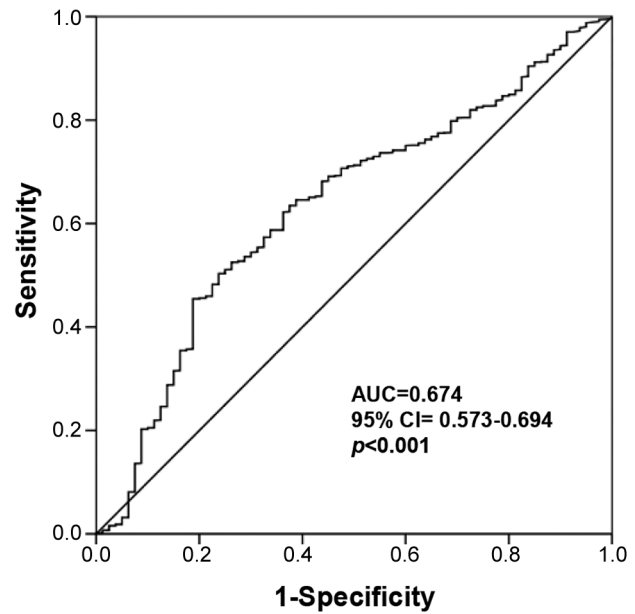


Figure 1. A: Receiver operating characteristic curve analysis to determine the optimal cut-off value of intraoperative blood loss (IBL) in patients who underwent potentially curative surgery for stage II pancreatic cancer. AUC: Area under the curve; CI: confidence interval.

under the curve=0.674; *p*<0.001, Figure 1). Patients were divided into groups with high (n=489) or low IBL (n=1,108). The clinicopathological features of the patients with low and high IBL are presented in Table I. There were significant differences in the tumor site, sex, body mass index (BMI), operative approach, tumor remnant, and pathological tumor depth. Compared with the low IBL group, the high IBL group had more male patients, rectal lesions, obese cases with a BMI of 30 kg/m² or more, laparotomy cases, more residual cancer and T4 cases.

Regarding the short-term outcomes of patients, the operative time was >3 hours in 23.5% of the patients in the high IBL group and in 10.4% of the patients in the low IBL group (*p*<0.001). Furthermore, the incidence of grade III or more postoperative complications in the group with high IBL was higher than that of the low IBL group (78.2% vs. 30.3%, *p*<0.001).

Evaluation of the effect of IBL on survival. Low IBL was associated with a significant survival benefit. The 5-year DFS rate was 77.8% and 63.4% for the low and high IBL groups, respectively (*p*<0.001) (Figure 2). The 5-year OS rates of the low and high IBL group was 96.7% and 93.4%, respectively (*p*=0.006) (Figure 3). Eight clinicopathological background factors were included in the multivariate analysis, which revealed that IBL was independently associated with both OS and DFS (Table II and Table III).

Table I. Comparison of clinicopathological factors according to intraoperative blood loss (IBL) using a cut-off of 200 ml.

Factor		IBL, n (%)		p-Value
		Low (n=1108)	High (n=489)	
Age	<75 Years	644	(58.0)	0.234
	≥75 Years	467	(42.0)	
Gender	Male	600	(54.2)	<0.001
	Female	508	(45.8)	
Lymph node metastasis	Absent	584	(52.6)	0.637
	Present	526	(47.4)	
Site of tumor	Colon	771	(77.2)	<0.001
	Rectum	228	(22.8)	
BMI	<30 kg/m ²	911	(98.1)	0.001
	≥30 kg/m ²	18	(1.9)	
Operation approach	Open	710	(63.9)	<0.001
	Lap, Rob	401	(36.1)	
Tumor remnant	R0	1075	(96.8)	<0.001
	R1	36	(3.2)	
Lymph node dissection	D2	530	(47.7)	0.569
	D3	580	(52.3)	
Complications (grade >III)	Absent	996	(89.6)	<0.001
	Present	115	(10.4)	
T-Factor	T1-3	811	(73.1)	0.009
	T4	298	(26.9)	
Operative time	<3 h	666	(61.7)	<0.001
	≥3 h	414	(38.3)	

BMI: Body mass index; Lap: laparoscopic-assisted; Rob: robotic-assisted.

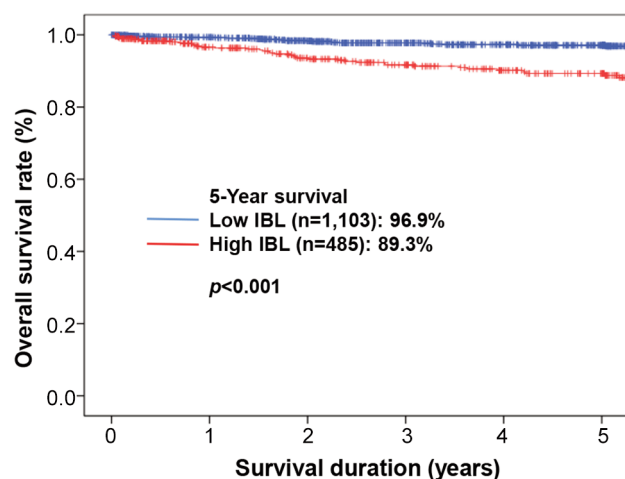


Figure 2. Recurrence-free survival rates in the groups with high (≥200 ml) and low (<200 ml) intraoperative blood loss (IBL). The study population consisted of patients who underwent potentially curative surgery for stage II/III colorectal cancer.

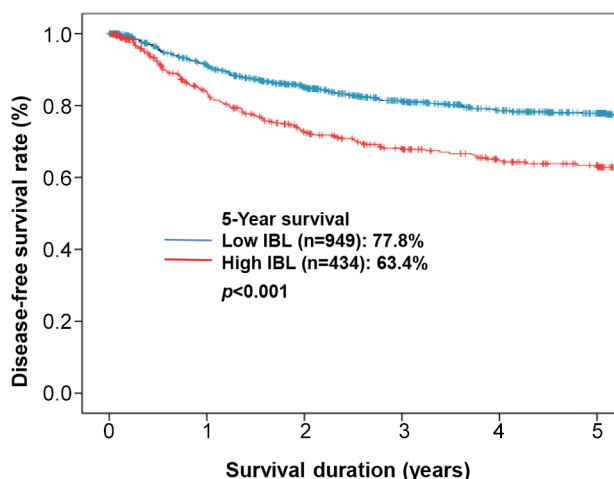


Figure 3. Overall survival rates in the high IBL (≥200 ml) and low IBL (<200 ml) groups. The study population consisted of patients who underwent potentially curative surgery for stage II/III colorectal cancer.

Recurrence patterns. The sites of initial recurrence are shown in Table IV. In both groups, liver metastasis was the most frequent type of recurrence. A chi-square test revealed that the rates of lymph node recurrence and local site recurrence were significantly higher in the group with high IBL ($p < 0.001$).

Discussion

In this study, which was based on a subgroup analysis of data from more than 1,500 cases, we showed that IBL ≥200 ml was an independent risk factor for poor OS and DFS, as

Table II. Univariate and multivariate Cox proportional hazards analysis of clinicopathological factors for disease-free survival of patients after colorectal cancer surgery.

Factor	Subgroup	Univariate analysis			Multivariate analysis		
		OR	95% CI	p-Value	OR	95% CI	p-Value
Age	<75 Years	1.000			1.000		
	≥75 Years	0.999	0.797-1.253	0.994	1.079	0.855-1.362	0.520
Gender	Male	1.000			1.000		
	Female	0.802	0.641-1.002	0.052	0.827	0.658-1.039	0.103
Lymph node metastasis	Absent	1.000			1.000		
	Present	2.526	2.001-3.189	<0.001	2.378	1.870-3.023	<0.001
T-Factor	T1-3	1.000			1.000		
	T4	2.614	2.102-3.250	<0.001	2.108	1.671-2.660	<0.001
Tumor remnant	R0	1.000			1.000		
	R1	2.370	1.676-3.351	<0.001	1.243	0.863-1.792	0.243
Operative approach	Open	1.000			1.000		
	Lap, Rob	0.744	0.562-0.986	0.040	0.929	0.673-1.282	0.652
Lymph node dissection	D2	1.000			1.000		
	D3	0.955	0.766-1.190	0.679	0.939	0.743-1.188	0.602
IBL	<200 ml	1.000			1.000		
	≥200 ml	1.803	1.442-2.255	<0.001	1.713	1.348-2.178	<0.001

IBL: Intraoperative blood loss; Lap: laparoscopic-assisted; Rob: robotic-assisted.

Table III. Univariate and multivariate Cox proportional hazards analysis of clinicopathological factors for overall survival of patients after colorectal cancer surgery.

Factor	Subgroup	Univariate analysis			Multivariate analysis		
		OR	95% CI	p-Value	OR	95% CI	p-Value
Age	<75 Years	1.000			1.000		
	≥75 Years	1.814	1.163-2.827	0.009	2.334	1.454-3.746	<0.001
Gender	Male	1.000			1.000		
	Female	0.636	0.400-1.012	0.056	0.755	0.468-1.218	0.250
Lymph node metastasis	Absent	1.000			1.000		
	Present	2.120	1.339-3.358	0.001	1.869	1.163-3.004	0.010
T-Factor	T1-3	1.000			1.000		
	T4	2.547	1.640-3.954	<0.001	1.739	1.080-2.799	0.023
Tumor remnant	R0	1.000			1.000		
	R1	4.206	2.448-7.226	<0.001	2.533	1.407-4.561	0.002
Operative approach	Open	1.000			1.000		
	Lap, Rob	0.680	0.374-1.237	0.206	0.629	0.308-1.285	0.204
Lymph node dissection	D2	1.000			1.000		
	D3	2.814	1.722-4.599	<0.001	2.894	1.739-4.816	<0.001
IBL	<200 ml	1.000			1.000		
	≥200 ml	3.403	2.154-5.376	<0.001	2.730	1.647-4.524	<0.001

IBL: Intraoperative blood loss; Lap: laparoscopic-assisted; Rob: robotic-assisted.

well as postoperative morbidity, in patients with stage II/III CRC who underwent radical surgery. The results support the hypothesis that IBL affects the long-term survival of patients with CRC.

In this study, there were significant differences in the distribution of tumor site, sex, body mass index, operative

approach, tumor remnant and pathological depth. The fact that male patients bled more was likely due to the fact that men have a narrower pelvis, which makes surgery more difficult. In the TNM classification, the T-stage may have influenced the amount of bleeding because surgery for advanced T-stage cancer is likely to require more extensive

Table IV. Comparison of patterns of recurrence between groups with high and low intraoperative blood loss (IBL) during colorectal cancer surgery.

Factor	All cases	IBL, n (%)		p-Value
		Low (n=88)	High (n=34)	
Site of recurrence				
Lymph node	53	25 (2.3)	28 (5.7)	<0.001
Local	70	29 (2.6)	41 (8.4)	<0.001
Distant site				
Lung	74	50 (4.5)	24 (4.6)	0.721
Liver	128	81 (7.3)	47 (9.6)	0.115
Bone	21	9 (0.8)	12 (2.5)	0.008
Disseminated				
Yes	54	33 (3.0)	21 (4.3)	0.117

dissection. The volume of IBL for patients with CRC and pre-existing anemia are the most important factors in decisions relating to blood transfusion. Blood transfusion has been demonstrated to increase the risk for complications (13), mainly infectious complications, as well as the risk for recurrence (14). It remains unclear why IBL is associated with morbidity and low survival. It has been reported, based on animal experiments, that the activity or cytotoxicity of natural killer cells was depressed after blood loss, and that the degree of reduction was correlated with the amount of blood loss (15, 16). IBL has been reported to be associated with the prognosis of several types of digestive carcinoma. In hepatocellular carcinoma, Katz *et al.* reported increased IBL during hepatic resection to be an independent prognostic factor for tumor recurrence and death (10). In pancreatic cancer, Tamagawa *et al.* showed that IBL $\geq 1,000$ ml was an independent risk factor for poor OS and DFS, as well as postoperative morbidity, in patients with stage II/III pancreatic cancer who underwent radical surgery (17). Nagai *et al.* also reported that IBL was a prognostic determinant of survival after surgery for pancreatic cancer and that operative blood loss can be used to stratify the risk of pancreatic cancer mortality (7). In gastric cancer, Liang *et al.* reported that IBL is an independent prognostic factor for gastric cancer after curative resection (8). Reducing IBL can improve the long-term outcomes of patients after curative gastrectomy for gastric cancer. Ito *et al.* also reported that IBL adversely influenced the long-term outcomes of patients with stage II/III gastric cancer (9). On the other hand, it was also reported that the minimization of IBL was very important but not an independent prognostic factor for patients with cancer (18, 19). There have been very few articles about the association between IBL and the long-term outcomes of CRC. Mörner *et al.* reported that the degree of blood loss during colon cancer surgery is a factor that influences long-term

survival (20) and Okumura *et al.* reported that a high volume of IBL significantly affects postoperative morbidity, OS, and recurrence in elderly patients with CRC (21). Regarding the site of recurrence in our study, the rates of lymph node recurrence and local site recurrence were significantly higher in the group with high IBL. This suggests that local resection and lymph node dissection for advanced cancer are inadequate for patients with high intraoperative bleeding.

The present study was associated with some limitations. Firstly, this was a retrospective study of a single study group; thus, the findings need to be confirmed in another large-scale prospective validation study. Secondly, there was no uniform threshold for IBL. Therefore, different statistical methods may obtain different values. The distribution of blood loss was divided into two groups using an optimal cut-off point (200 ml) for classification based on the ROC curve analysis. Previous reports discussing the relationship between long-term prognosis and bleeding volume in patients during surgery for CRC reported using cut-off values of 200-800 ml (20-22). Thirdly, the performance of different postoperative therapies might have had a confounding effect.

In conclusion, the long-term outcomes, such as OS and DFS, of patients with stage II/III CRC who underwent curative resection significantly differed according to the amount of IBL. The results of this study suggest that the reduction of IBL has the potential to improve the prognosis of patients with stage II/III CRC.

Conflicts of Interest

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

Authors' Contributions

All Authors contributed to the study conception and design. Data collection was performed by all Authors. The statistical analysis was performed by Toru Aoyama. The first draft of the article was written by Hiroshi Tamagawa, and all Authors commented on previous versions of the article. All Authors read and approved the final article.

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