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ORIGINAL ARTICLE

Negative impact of intraoperative blood loss on long-term outcome after curative gastrectomy for advanced gastric cancer: exploratory analysis of the JCOG1001 phase III trial

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Abstract

Background Recent retrospective studies have shown that increased intraoperative blood loss (IBL) during curative gastrectomy for patients with advanced gastric cancer is a negative prognostic indicator for recurrence. However, there are no reliable reports assessing this with a large-scale prospective cohort. This study aimed to evaluate the impact of IBL on long-term outcomes using data from the JCOG1001 phase III trial, which was designed to determine if bursectomy led to improved survival vs. nonbursectomy in patients with cT3/4a gastric cancer.

Methods This study included 1203 of the 1204 patients enrolled in the JCOG1001. From the tertiles of IBL (196 ml, 400 ml), we divided the patients into three groups: IBL < 200 ml representing small blood loss (SBL, $n = 404$), 200 ml ≤ IBL < 400 ml representing medium blood loss (MBL, $n = 393$), and IBL ≥ 400 ml representing large blood loss (LBL, $n = 406$). The impact of IBL on relapse-free survival (RFS) was evaluated with univariable comparisons and multivariable Cox regression analyses.

Results Three-year RFS after SBL, MBL, and LBL was 81.7%, 74.8%, and 70.6%, respectively. Multivariable analysis identified IBL, Eastern Cooperative Oncology Group performance status, pT, pN, and postoperative adjuvant chemotherapy as independent predictors of RFS. Compared with SBL as a reference, the hazard ratios of MBL and LBL were 1.461 ($P = 0.012$) and 1.520 ($P = 0.009$), respectively.

Conclusions Based on the analysis of data from a large-scale prospective study, an IBL of ≥ 200 ml after curative surgery for patients with cT3/4a gastric cancer was an independent predictor of reduced RFS.

Keywords Gastric cancer · Gastrectomy · Prognosis · Blood loss · Surgical

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Introduction

Gastric cancer is one of the most common causes of cancer-related death in the world [1, 2]. Radical gastrectomy with regional lymph node dissection is the only potentially curative treatment for patients with advanced gastric cancer. Gastrectomy with D2 lymph node dissection is the standard of practice for locally advanced gastric cancer in both Western and Asian countries. However, lymph node dissection around major blood vessels is technically demanding and challenging for surgeons, and excessive intraoperative blood loss (IBL) can occur even at the hands of experienced surgeons.

The impact of IBL on long-term postoperative outcomes in patients with cancer, not just gastric cancer, has long been of interest in the field of surgical oncology [3–7]. The adverse effect of IBL on the prognosis of patients with gastric cancer was first reported by Dhar et al. [8] in 2000. Their retrospective analysis of 152 patients with transmural advanced gastric cancer found that IBL > 500 ml was an independent prognostic factor of long-term survival. Several subsequent works also identified excessive IBL as predictive of a worse prognosis with different cutoff values assigned by each [9–13], while others did not associate IBL with outcome [14–16]. The issue of IBL and prognosis, while well studied, is unsettled. Common limitations of previous studies were their retrospective, single-center nature. The topic lacks a reliable report that utilizes a prospective cohort in which the patients, the surgical procedure, postoperative adjuvant chemotherapy, and follow-up were strictly defined.

The Japan Clinical Oncology Group study 1001 (JCOG1001) was a large-scale, multicenter, randomized phase III trial created to assess the efficacy of bursectomy in patients with locally advanced gastric cancer [17]. A total of 1204 patients were registered in this trial and randomly assigned to bursectomy or nonbursectomy treatment. While the trial failed to demonstrate survival superiority after bursectomy to nonbursectomy for cT3/4 gastric cancer, its homogeneity makes it an important resource for additional analysis of this population. The objective of the present study was to evaluate the impact of IBL on long-term outcomes after curative gastrectomy using data from the JCOG1001 phase III trial.

Methods

Patients

Between June 1, 2010, and March 30, 2015, 1204 patients registered in the JCOG1001 were randomly assigned (1:1) during surgery for either an omentectomy alone (nonbursectomy) or a bursectomy ($n = 602$ for each group). Trial eligibility criteria and the method of randomization have been previously reported in detail [17]. In brief, patients 20–80 years of age with histologically proven and resectable primary gastric carcinoma with an estimated depth of cT3(SS) or cT4(SE) were enrolled. Patients with distant metastases, bulky lymph nodes or Borrmann type 4 or large (≥ 8 cm) type 3 carcinomas were excluded. Fifty-seven Japanese hospitals participated in the trial. JCOG1001 was registered with UMIN-CTR, number UMIN000003688. The study protocol of JCOG1001 was approved by the JCOG Clinical Trial Review Committee and the institutional review boards of all participating institutions. The procedures were conducted in accord with the ethical standards of the Helsinki Declaration of 1975.

At the second planned interim analysis on September 17, 2016, the JCOG Data and Safety Monitoring Committee independently reviewed the results of the trial and recommended early termination of the study for futility because overall survival was lower in the bursectomy group than the nonbursectomy group. The study was terminated early at that time.

Of the 1204 patients, 1 patient did not receive a gastrectomy because of peritoneal metastases were identified after randomization. The remaining 1203 patients were included in the present analysis.

Surgical procedures and postoperative treatment

All patients received either a total or distal gastrectomy by laparotomy with D2 lymph node dissection as dictated by the Japanese gastric cancer treatment guidelines (third edition) [18]. Those patients who required a total gastrectomy for cT2 or deeper tumors in the proximal third of the stomach also had their spleen removed to complete a splenic hilar lymphadenectomy. An omentectomy was done in both groups in this trial. In the bursectomy group only the peritoneal lining of the bursa omentalis was removed en bloc to the greatest extent possible from the anterior plane of the transverse mesocolon and the pancreas. The bursa omentalis peritoneal lining was preserved as much as possible in the nonbursectomy group. Postresection reconstruction type was not specified in the protocol.

IBL was measured according to the volume and weight of blood absorbed by surgical gauze and suction pumps during the gastrectomy. IBL was extracted from the operative and anesthesia records of each patient. Perioperative allogeneic blood transfusion was defined as the administration of blood cells from the start of surgery to the next morning. General indications for transfusion were hemoglobin concentration < 8.0 g/dl or hemodynamic changes during surgery, although transfusions were performed at the discretion of

the anesthesiologist and the surgical team responsible for perioperative care.

Postoperative adjuvant chemotherapy with S-1 for 1 year was performed as a protocol treatment for patients who had complete tumor resection and pathologic Stage IIA, IIB, IIIA, IIIB or IIIC tumors except for pT1 and pT3 (SS) N0 tumors, according to the Japanese gastric cancer treatment guidelines (third edition) [18]. After protocol completion, no further treatment was given unless the tumor recurred. All clinical data were obtained from the JCOG1001 case report forms.

Follow-up

Postoperative follow-up was on a fixed schedule. A contrast-enhanced abdominal computed tomography was done every 6 months for 3 years, and yearly thereafter. Carcinoembryonic antigen and carbohydrate antigen 19–9 levels were drawn every 3 months for 3 years, and every 6 months thereafter. Upper endoscopy (only for distal gastrectomy cases) and chest X-ray were done every year. The median follow-up was 4.0 (interquartile range [IQR] 2.6–5.0) years, and the last follow-up date was November 29, 2016. Relapse-free survival (RFS) was the time from the date of randomization during surgery to the date of the first disease recurrence or death from any cause. Overall survival (OS) was the time from the date of randomization during surgery to the date of death from any cause. Data collection for patients who did not experience an event was completed on the date of the final observation.

Statistical analysis

Fisher's exact test was performed for categorical variables and the Mann–Whitney *U* test was used for continuous variables. Survival was estimated using the Kaplan–Meier method, and differences between survival curves were compared using the log-rank test. The Cox proportional hazards model was used to evaluate the hazard ratio relative to each variable. Univariable and multivariable analyses with a Cox regression model were performed to identify variables that influenced RFS. Variables of interest included IBL ($<200/200\leq$ and $<400/\geq 400$ ml), age ($\leq 65/>65$ years), sex (male/female), body mass index (BMI) ($<22.7/\geq 22.7$ kg/m^2), histological type (undifferentiated type/differentiated type), Eastern Cooperative Oncology Group performance status (PS) (0/1), surgical procedure (distal gastrectomy/total gastrectomy), combined organ resection except for cholecystectomy (performed/not performed), bursectomy (performed/not performed), extent of lymphadenectomy ($\leq$D2/$\geq$D2+), operation time ($<238/\geq 238$ min), blood transfusion (no/yes), tumor size ($<5.2/\geq 5.2$ cm), pT (T1/2/3/4), pN (N0/1/2/3), and postoperative adjuvant chemotherapy (no/yes). All *P* values less than 0.05 were considered statistically significant. Statistical analyses were done with SAS version 9.2 or higher.

Results

Patient characteristics are shown in Table 1. A total gastrectomy was performed on 416 patients (34.6%). Fifty-six patients (4.7%) received blood transfusions. The median IBL was 285 ml (range 0–3068 ml). The first tertile (33.3 percentile) was 196 ml, and the second tertile (66.7 percentile) was 400 ml. On the basis of these tertiles, we divided all 1203 patients into 3 groups: IBL < 200 ml defined as small blood loss (SBL, $n=404$), 200 ml ≤ IBL < 400 ml defined as medium blood loss (MBL, $n=393$), and IBL ≥ 400 ml defined as large blood loss (LBL, $n=406$). Median (range) IBL was 110 ml (0–199) in SBL, 283 ml (200–398) in MBL, and 575 ml (400–3068) in LBL. There were significant differences between the groups in age, sex, BMI, PS, surgical procedure, combined organ resection except for cholecystectomy, bursectomy, operative time, blood transfusions required, tumor size, and pathological T status. However, tumor histology, past surgical history, the extent of lymphadenectomy, pathological N status, pathological stage, and the proportion of patients receiving adjuvant chemotherapy were not different.

A total of 283 recurrences were reported. The most frequent first recurrent site was the peritoneum, followed by the lymph nodes and liver (Table 2). RFS curves of the three IBL groups are shown in Fig. 1. The 3-year RFS after SBL, MBL, and LBL were 81.7% (95% confidence interval [CI] 77.3–85.2), 74.8% (95% CI 70.0–79.0), and 70.6% (95% CI 65.7–74.9) respectively, which were significantly different between the three groups (log-rank two-sided $P=0.002$). Compared with SBL as a reference, the hazard ratio (HR) for RFS of MBL was 1.351 (95% CI 1.016–1.796, $P=0.038$) and that of LBL was 1.635 (95% CI 1.243–2.150, $P<0.001$). The 3-year OS after SBL, MBL, and LBL were 88.9% (95% CI 85.2–91.7), 83.6% (95% CI 79.2–87.1), and 81.3% (95% CI 77.0–84.9), which were significantly different among the three groups (log-rank two-sided $P=0.014$) (Online Resource 1).

Multivariable analysis revealed that IBL was an independent risk factor for recurrence, together with PS, pT status, pN status, and postoperative adjuvant chemotherapy. Bursectomy, blood transfusion, and combined organ resection except for cholecystectomy were not independent risk factors (Table 3). Compared with SBL as a reference, the HR of MBL was 1.461 (95% CI 1.088–1.962, $P=0.012$) and that of LBL was 1.520 (95% CI 1.108–2.083, $P=0.009$).

Table 1 Clinicopathological characteristics of SBL, MBL and LBL

	SBL (< 200 ml) $n = 404$	MBL (≥ 200 ml, < 400 ml) $n = 393$	LBL (≥ 400 ml) $n = 406$	*P* value
Age, median [IQR] (range)	64 [59–71] (31–80)	66 [59–72] (29–80)	67 [61–72] (29–80)	0.002
≤ 65 years	219	190	176	0.008
≥ 66 years	185	203	230	
Sex				
Male	233	280	333	< 0.001
Female	171	113	73	
BMI, median [IQR] (range)	21.6 [19.8–23.9] (15.6–29.9)	22.8 [20.7–24.8] (15.5–29.6)	23.6 [21.7–25.5] (14.9–29.8)	< 0.001
< Median [22.7]	253	189	153	< 0.001
≥ Median [22.7]	151	204	253	
ECOG performance status				
0	393	384	384	0.032
1	11	9	22	
Histological type				
Undifferentiated type	187	189	187	0.821
Differentiated type	217	204	219	
Past surgical history				
No	314	305	292	0.089
Yes	90	88	114	
Surgical procedure				
Distal gastrectomy	302	274	211	< 0.001
Total gastrectomy	102	119	195	
Combined organ resection except for cholecystectomy				
No	330	290	240	< 0.001
Yes	74	103	166	
Resected organs[a]				
Spleen	71	97	162	
Gall bladder	80	117	132	
Pancreas	3	3	8	
Others	4	6	10	
Bursectomy				
No	246	197	166	< 0.001
Yes	158	196	240	
Extent of lymphadenectomy				
≤ D2 (11 patients with D1)	281	274	296	0.499
≥ D2 +	123	119	110	
Operation time (min), median [IQR] (range)	203.5 [162.5–244] (80–630)	238 [200–279] (123–439)	271.5 [232–316] (135–473)	< 0.001
Blood loss (ml), median [IQR] (range)	110 [68–150] (0–199)	283 [230–330] (200–398)	575 [470–770] (400–3068)	< 0.001
Blood transfusion				
No	401	384	362	< 0.001
Yes	3	9	44	
Tumor size (cm), median [IQR] (range)	5.0 [4.0–6.5] (1.5–16.0)	5.0 [4–6.5] (1.8–13.0)	5.8 [4.5–7.0] (1.5–17.0)	< 0.001
pT status				
pT1	29	32	25	0.018
pT2	59	64	46	
pT3	145	159	193	
pT4	171	138	142	
pN status				
pN0	137	124	110	0.485

Table 1 (continued)

	SBL (< 200 ml) $n = 404$	MBL (≥ 200 ml, < 400 ml) $n = 393$	LBL (≥ 400 ml) $n = 406$	*P* value
pN1	77	79	85	
pN2	95	81	92	
pN3a	64	72	75	
pN3b	31	37	44	
Pathological stage				
I	103	112	99	0.356
II	117	103	118	
III	146	152	143	
IV	78	26	46	
Adjuvant chemotherapy				
No	157	153	163	0.915
Yes	247	240	243	

SBL small blood loss, *MBL* medium blood loss, *LBL* large blood loss, *IQR* interquartile range, *BMI* Body Mass Index, *ECOG* Eastern Cooperative Oncology Group

[a]There was some overlap among the patients

Table 2 First recurrent sites

	SBL (< 200 ml) $n = 404$	MBL (≥ 200 ml, < 400 ml) $n = 393$	LBL (≥ 400 ml) $n = 406$
Any site	75	99	109
Peritoneum	36	45	43
Lymph nodes	24	25	31
Liver	16	21	32
Lung	2	9	6
Bone	2	2	2
Others	18	16	14

There was some overlap among the patients

SBL small blood loss, *MBL* medium blood loss, *LBL* large blood loss

Discussion

The impact of IBL on the long-term outcome of gastric cancer patients has long been the focus of attention, and several retrospective data have been reported. We sought to elucidate whether IBL was associated with the long-term outcome of patients with locally advanced gastric cancer using data from the JCOG1001, a large-scale, multicenter, randomized phase III trial. The JCOG1001 was terminated early after the second interim analysis, which was conducted 1.5 years after the last patient was enrolled, and the follow-up period was not long enough. Therefore, multivariable analyses were performed using RFS as the endpoint, which can assess long-term outcomes in a shorter period. Our results indicated that an IBL ≥ 200 ml was significantly associated with a shorter RFS, and IBL was an independent risk factor for disease recurrence after curative gastrectomy. This is the first study to report a negative impact of IBL on the long-term outcome of patients with gastric cancer using data from a large-scale, multicenter, prospective cohort.

The median IBL for all 1203 patients was 285 ml, which was similar to what was reported by previous studies [10, 12, 13, 15]. Increased IBL was associated with male sex, higher BMI, larger tumor size, total gastrectomy, and cases where combined organ resection was required, correlations also similar to previous reports. We selected 200 ml and 400 ml as IBL cutoff points for our analyses because these were nice round numbers for surgeons to recognize and were also located around our predicted optimal cutoff value, which we estimated would be in the range of 200–500 ml as identified in previous studies [8–13]. IBL ≥ 200 ml was identified as an independent risk factor for reduced RFS, which is the lowest IBL threshold ever reported.

The JCOG1001 showed that a bursectomy did not provide a survival advantage over nonbursectomy in the treatment of patients with resectable advanced gastric cancer [17]. OS and RFS were slightly lower in the bursectomy group than the nonbursectomy group, and a pancreatic fistula was significantly more common in the bursectomy group than in the nonbursectomy group (5% vs. 2%; $P = 0.032$). We speculated that a possible cause of the negative results of this trial was the growth stimulation of residual cancer cells by inflammatory cytokines and growth factors induced by surgical stress or postoperative complications [17, 19]. In fact, in a prior exploratory analysis of the JCOG1001 we reported that postoperative complications adversely affected

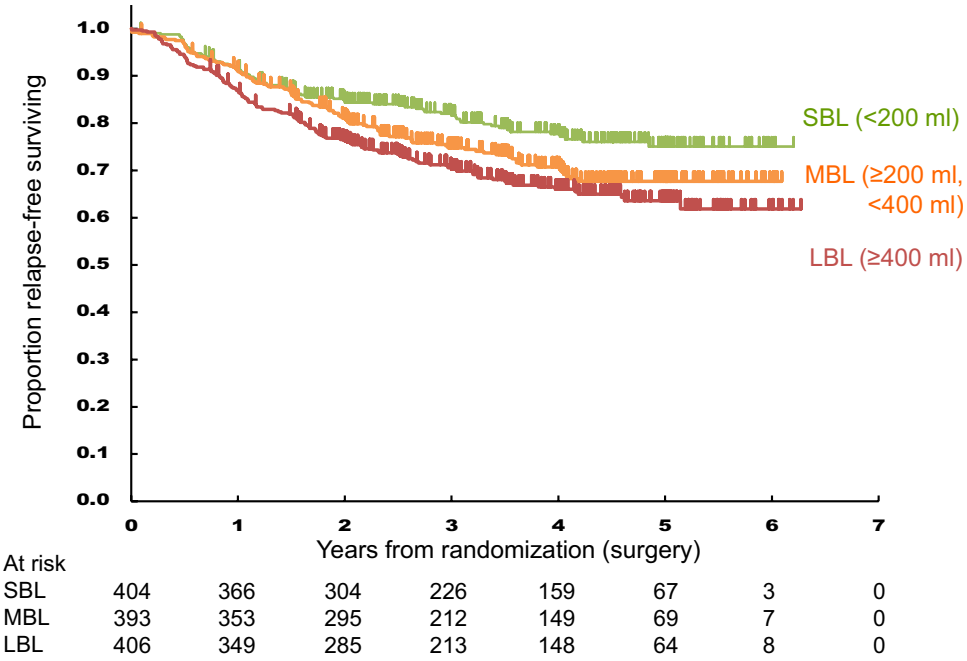

Fig. 1 Relapse-free survival by intraoperative blood loss

long-term survival [20]. On the other hand, the median IBL in the bursectomy group was 330 ml (IQR 183–530), which was 100 ml greater than that in the nonbursectomy group (230 ml [IQR 130–410]; $P < 0.0001$). One of the causes of the negative results in JCOG1001 might be the greater IBL in the bursectomy group.

There were several studies that reported on the adverse effects of IBL on long-term outcomes, for which they discussed several possible causes. One possible cause is the spillage of cancer cells into the peritoneal cavity due to significant bleeding during surgery. Peritoneal recurrence is thought to be caused by this mechanism. Kamei et al. [9] reported that an IBL of ≥ 475 mL was specifically associated with the development of a peritoneal recurrence after curative gastrectomy in 146 patients with advanced gastric cancer. Arita et al. [11] investigated 540 patients undergoing curative gastrectomy and reported that a high IBL correlated with a higher risk of peritoneal recurrence. Moreover, in the laboratory setting they confirmed that the ability of gastric cancer cells and mesothelial cells to adhere to each other was increased in the presence of blood plasma.

Second possible way that IBL can influence survival is through antitumor immunosuppression induced by excessive IBL. Bruns et al. [4] reported that the activity of natural killer cells was significantly decreased in patients with an IBL of more than 700 ml during upper gastrointestinal surgery compared to those who lost less than 500 ml. Miki et al. [21] reported that interleukin (IL)-6 and IL-6-triggered tumor growth factors were increased in patients with colorectal cancer receiving blood transfusion because of excessive IBL, which was associated with a poor prognosis. In several previous studies that reported a relationship between IBL and survival immunosuppression was thought to be the primary reason why bleeding was associated with recurrence, especially via hematogenous spread [9, 10, 13].

Third, perioperative blood transfusions and postoperative complications may adversely affect long-term outcomes as confounders of excessive IBL. In general, excessive IBL increases the need for blood transfusions, and patients with increased IBL are at greater risk of subsequent postoperative complications. Several studies have reported on the negative impact of blood transfusions and complications on RFS [14, 16, 22–24], and Nakanishi et al. reported in their review article that postoperative complications and blood transfusions may have a negative impact on long-term outcomes [25]. In the present study less than 5% of all patients required a blood transfusion, with 2.3% (9/393) of the MBL group requiring a transfusion even though it was above the IBL threshold (≥ 200 ml) predictive of a negative survival impact. In multivariable analysis, transfusion was not a significant prognostic factor (HR 0.919, $P = 0.730$). These results negatively indicate that transfusions may have affected long-term outcomes and support the conclusion that excessive IBL itself had an adverse effect on long-term outcome.

In contrast, in the present study, the group with greater IBL had more postoperative complications (Online Resource 2). In our other exploratory analysis, Clavien–Dindo (C–D) complications of Grade III and above were associated with poor RFS and were identified as the most suitable definition of complication for predicting negative long-term survival outcomes [20]. Excessive IBL may have induced complications, which in turn may

Table 3 Results of unevaluable and multivariable analysis for relapse-free survival (RFS)

Variables	Category	Events/*n*	3y-RFS (95% CI)	Univariable analysis		Multivariable analysis	
				HR (95% CI)	*P* value	HR (95% CI)	*P* value
Intraoperative blood loss							
	SBL (< 200 ml)	84/404	81.7 (77.3–85.2)	1		1	
	MBL (≥ 200 ml, < 400 ml)	109/393	74.8 (70.0–79.0)	1.351 (1.016–1.796)	0.038	1.461 (1.088–1.962)	0.012
	LBL (≥ 400 ml)	131/406	70.6 (65.7–74.9)	1.635 (1.243–2.150)	< 0.001	1.520 (1.108–2.083)	0.009
Age							
	≤ 65 years old	147/585	77.3 (73.6–80.6)	1		1	
	≥ 66 years old	177/618	74.0 (70.2–77.5)	1.206 (0.969–1.501)	0.093	1.104 (0.879–1.386)	0.395
Sex							
	Male	231/846	75.2 (72.1–78.1)	1		1	
	Female	93/357	76.6 (71.7–80.8)	0.904 (0.711–1.150)	0.411	0.954 (0.734–1.241)	0.728
BMI							
	< Median [22.7]	182/595	72.5 (68.6–76.1)	1		1	
	≥ Median [22.7]	142/608	78.7 (75.1–81.9)	0.757 (0.608–0.943)	0.013	0.810 (0.641–1.024)	0.078
Histological type							
	Undifferentiated type	161/563	74.4 (70.4–77.9)	1		1	
	Differentiated type	163/640	76.7 (73.1–80.0)	0.888 (0.714–1.104)	0.285	0.901 (0.715–1.135)	0.376
ECOG performance status							
	0	305/1161	76.2 (73.5–78.6)	1		1	
	1	19/42	59.1 (41.9–72.8)	2.068 (1.301–3.287)	0.002	1.942 (1.193–3.163)	0.008
Surgical procedure							
	Distal gastrectomy	195/787	77.6 (74.4–80.5)	1		1	
	Total gastrectomy	129/416	71.9 (67.1–76.1)	1.281 (1.026–1.600)	0.029	1.175 (0.780–1.769)	0.441
Combined organ resection except for cholecystectomy							
	No	217/860	76.8 (73.7–79.6)	1		1	
	Yes	107/343	72.9 (67.8–77.4)	1.189 (0.943–1.498)	0.144	0.891 (0.583–1.361)	0.592
Bursectomy							
	No	166/609	76.4 (72.7–79.7)	1		1	
	Yes	158/594	74.8 (70.9–78.2)	0.984 (0.792–1.224)	0.887	0.995 (0.792–1.252)	0.969
Extent of lymphadenectomy							
	≤ D2	218/851	76.0 (72.9–78.9)	1		1	
	≥ D2 +	106/352	74.7 (69.7–79.1)	1.123 (0.890–1.417)	0.327	0.962 (0.754–1.227)	0.753
Operation time (min)							
	< Median [238]	136/595	79.2 (75.5–82.4)	1		1	
	≥ Median [238]	188/608	72.2 (68.3–75.7)	1.381 (1.107–1.721)	0.004	1.186 (0.919–1.529)	0.190
Blood transfusion							
	No	304/1147	75.8 (73.1–78.3)	1		1	
	Yes	20/56	71.6 (57.3–81.9)	1.395 (0.887–2.193)	0.149	0.913 (0.566–1.473)	0.710
Tumor size (cm)							
	≤ median [5.2]	124/598	81.0 (77.4–84.0)	1		1	
	≥ median [5.2]	200/605	70.4 (66.4–74.0)	1.689 (1.350–2.113)	< 0.001	1.114 (0.879–1.413)	0.372
pT status							
	pT1	3/86	98.7 (91.4–99.8)	1		1	
	pT2	23/169	88.3 (82.3–92.4)	4.015 (1.206–13.374)	0.024	4.546 (1.354–15.264)	0.014
	pT3	108/497	81.0 (77.1–84.3)	6.603 (2.097–20.796)	0.001	5.616 (1.756–17.958)	0.004
	pT4	190/451	61.0 (56.2–65.5)	14.881 (4.757–46.556)	< 0.001	9.316 (2.920–29.717)	< 0.001
pN status							
	pN0	38/371	91.6 (88.1–94.1)	1		1	
	pN1	40/241	85.0 (79.5–89.0)	1.693 (1.086–2.640)	0.020	2.170 (1.352–3.485)	0.001
	pN2	84/268	73.7 (67.8–78.8)	3.337 (2.275–4.896)	< 0.001	3.392 (2.220–5.183)	< 0.001
	pN3a-pN3b	162/323	52.2 (46.4–57.7)	6.637 (4.660–9.454)	< 0.001	5.824 (3.909–8.678)	< 0.001

Table 3 (continued)

Variables	Category	Events/*n*	3y-RFS (95% CI)	Univariable analysis		Multivariable analysis	
				HR (95% CI)	*P* value	HR (95% CI)	*P* value
Adjuvant chemotherapy							
	No	125/473	76.0 (71.7–79.7)	1		1	
	Yes	199/730	75.4 (72.0–78.5)	0.996 (0.796–1.246)	0.973	0.528 (0.411–0.679)	< 0.001

CI confidence interval, *HR* hazard ratios, *SBL* small blood loss, *MBL* medium blood loss, *LBL* large blood loss, *BMI* Body Mass Index, *ECOG* Eastern Cooperative Oncology Group

have led to poor long-term survival. It is also possible that there were other confounding factors that may affect both excessive IBL and postoperative complications, such as surgical difficulty or tumor factors other than tumor size, pT or pN status. Further research is needed to answer these questions.

Reducing the incidence of postoperative complications may be more difficult for surgeons than reducing IBL. In the JCOG1001, 67% of the total patients had an IBL ≥ 200 ml, and 23% and 10% had C–D complications equal to or more than Grade II and Grade III, respectively. Since the number of patients with complications was not as large as those with greater IBL, and since surgeons are constantly careful and make efforts during surgery to avoid complications, it is never easy to improve long-term outcomes by further reducing complications. It is possible to reduce the IBL through the use of sealing devices, such as ultrasonically activated shears, [26, 27] or careful procedures even if they require longer operation time. Laparoscopic approaches including a robotic gastrectomy could also reduce IBL [28–31].

The present study has several limitations. First, it was unclear whether IBL adversely affects long-term survival in patients with poor prognostic factors, such as bulky lymph nodes or Borrmann type 4 or large type 3 carcinomas, which were excluded in the JCOG1001. Second, the mechanism behind RFS and excessive IBL has not been elucidated, and it is unclear whether IBL itself causes frequent relapses or adversely affects RFS through postoperative complications, or whether IBL is a surrogate for the other factors impacting RFS, although the present study showed that IBL during a curative gastrectomy was associated with more frequent recurrence. Further basic and clinical investigations to elucidate the mechanism are needed. Third, the present study did not include patients who underwent minimally invasive surgeries (MIS), such as a laparoscopic or robotic gastrectomy. MIS can be expected to reduce the amount of bleeding, and it is therefore of great interest to see whether MIS actually has less of an adverse effect on long-term outcomes due to reduced IBL.

In conclusion, the negative impact of IBL on long-term outcome after curative gastrectomy was confirmed by analyzing data from a large-scale prospective study. An IBL of 200 ml or more was significantly associated with poor long-term survival in this patient group. While external validation is required, we encourage surgeons to reduce IBL below 200 ml as much as possible to achieve a better outcome for patients with advanced gastric cancer.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent to be included in the study, or the equivalent, was obtained from all patients.

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