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The Impact of Intraoperative Blood Loss on the Survival of Patients With Stage II/III Pancreatic Cancer

HIROSHI TAMAGAWA[1,2], TORU AOYAMA[2], NAOTO YAMAMOTO[1], MARIKO KAMIYA[1], MASAAKI MURAKAWA[1], YOSUKE ATSUMI[2], MASAKATSU NUMATA[2], KEISUKE KAZAMA[2], KENTARO HARA[2], NORIO YUKAWA[2], YASUSHI RINO[2], MUNETAKA MASUDA[2] and SOICHIRO MORINAGA[1]

[1]*Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan;*
[2]*Department of Surgery, Yokohama City University, Yokohama, Japan*

Abstract. *Background: Pancreatic cancer is a fatal disease with a poor prognosis. Pancreatic cancer is often unresectable at the time of diagnosis, so the analysis of risk factors in patients with indications for surgery is important. We investigated the impact of intraoperative blood loss (IBL) on survival and recurrence in patients with stage II/III pancreatic cancer after curative surgery. Patients and Methods: This study included 76 patients who underwent curative surgery for stage II/III pancreatic cancer between 2007 and 2012. The risk factors for overall (OS) and recurrence-free (RFS) survival were identified. Results: IBL of 1,000 ml was considered to be the optimal cut-off value for classification based on a receiver operating characteristic (ROC) curve analysis. The OS rates at 5 years after surgery in the groups with low and high IBL were 36.6% and 11.4%, respectively, which was a statistically significant difference (p=0.003). The RFS rates at 1 year after surgery were 49.8% and 24.6%, respectively, which was a significant difference (p=0.045). A multivariate analysis demonstrated that IBL was a significant independent risk factor for OS. Conclusion: IBL is an independent prognostic factor after curative resection of stage II/III pancreatic cancer. The reduction of bleeding during surgery is necessary to improve the results of pancreatic cancer surgery.*

*These Authors contributed equally to this study.

Correspondence to: Hiroshi Tamagawa, Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 2-3-2 Nakao, Asahi-ku, Yokohama 241-8515, Japan. E-mail: rinta77-nosuke@amber.plala.or.jp and Toru Aoyama, Department of Surgery, Yokohama City University, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan. E-mail: t-aoyama@lilac.plala.or.jp

Key Words: Pancreatic cancer, Intraoperative blood loss, survival, recurrence.

Pancreatic cancer, which had a 5-year survival rate of less than 5% in 2012, is a major cause of death from cancer worldwide (1, 2). Complete resection is essential for obtaining a cure in patients with pancreatic cancer. However, such patients suffer recurrence, even after complete curative resection followed by adjuvant treatment (2-4). The Japan Adjuvant Study Group of Pancreatic Cancer showed that S-1 adjuvant chemotherapy improved the overall (OS) and recurrence-free (RFS) survival of patients who underwent complete resection of pancreatic cancer, with 3-year OS and 5-year disease-free survival rates of 22.6% and 44.1%, respectively (5).

Thus, the identification of prognostic factors for pancreatic cancer is important in order to select candidates for more aggressive treatment. Various kinds of clinicopathological factors, including the tumor size, lymph node metastasis, resection margin status, and histological type, have been reported to be significant prognostic factors that can be used to predict survival in patients with pancreatic cancer (6-8). A number of potential prognostic factors have been reported, such as intraoperative blood loss (IBL) and perioperative blood transfusion. Burrows and Tartter reported the risk associated with perioperative blood transfusion in patients with colorectal cancer for the first time in 1982 (9). In gastric cancer, Kaneda *et al*. reported that blood transfusion was associated with a poor outcome (10). Similarly, IBL increases the risk of postoperative recurrence and worsens the prognosis in patients with several types of cancer (9-10). However, there are still few articles about the association between IBL and long-term outcomes of patients with pancreatic cancer.

In the present study, we investigated whether the OS and RFS of patients who underwent curative surgery for pancreatic cancer were affected by IBL.

Patients and Methods

Patients. Consecutive patients (n=76) who underwent pancreatic surgery at Kanagawa Cancer Center from 2007 to 2012 were enrolled retrospectively. The inclusion criteria were as follows: A common pathological type of pancreatic cancer and staged according

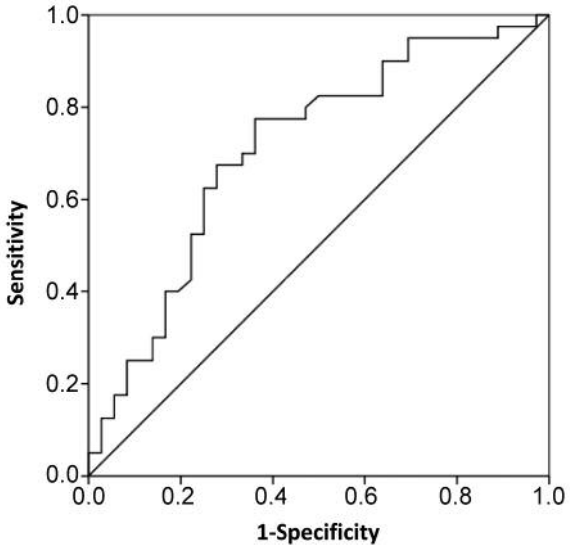

Figure 1. *The receiver operating characteristic curve analysis to determine the optimal cut-off value of intraoperative blood loss (IBL) in patients who underwent potentially curative surgery for stage II/III pancreatic cancer. Area under the curve=0.74, 95% confidence interval=0.592-0.829; p=0.002.*

to the seventh edition of the Union for International Cancer Control (UICC) TNM classification; and curative resection as the initial treatment for pancreatic cancer. Patients with other pancreatic and periampullary neoplasms such as cystadenocarcinoma, endocrine tumors, or intraductal papillary mucinous neoplasms, were excluded from the present study.

Surgical procedure. All surgeries were performed at the Pancreatic Unit in Kanagawa Cancer Center and performed in accordance with standardized procedures that have been described elsewhere (11-14). Briefly, in cases of pancreatoduodenectomy, we performed subtotal stomach-preserving pancreatoduodenectomy as the standard procedure.

Adjuvant chemotherapy. Treatment with gemcitabine (a weekly dose of 1,000 mg/m^2 for 3 weeks, followed by 1 week of rest) was initiated within 8 weeks after surgery for 6 months after surgery or S-1 chemotherapy (80 mg/m^2/day of S-1 for 4 weeks, followed by 2 weeks of rest) was also started within 8 weeks after curative surgery and continued for 24 weeks for 6 months after surgery (15, 16).

Follow-up. All patients were followed-up for 5 years after curative surgical resection. The serum Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels and radiological examination by computed tomography were checked at least every 3 months for 5 years at outpatient clinics.

Evaluations and statistical analyses. The appropriate cut-off point for IBL was determined based on a receiver operating characteristic (ROC) curve analysis. The significance of the associations between IBL and clinicopathological parameters was determined using the chi-squared test or Fisher's exact test. OS was defined as the period from surgery until death. RFS was defined as the period from surgery until recurrence or death. The Kaplan-Meier method was used to create the OS and RFS curves, and these were compared using the log-rank test. Independent prognostic factors were identified by the Cox proportional hazards regression model. *p*-Values of less than 0.05 were considered statistically significant. The statistical analysis was performed using the SPSS statistical program ver 23.0 (IBM, Armonk, NY, USA). The SPSS software program (ver23.0 J Win; IBM, Armonk, NY, USA) was used for all of the statistical analyses. This study was approved by the IRB Committee of the Kanagawa Cancer Center (Epidemiology-32).

Table I. *Comparison of intraoperative blood loss (IBL) according to clinicopathological factors.*

		IBL group, n (%)		
	Total, n	Low	High	*p*-Value
Age				
<70 Years	44	20 (45.5)	24 (54.5)	0.902
≥70 Years	32	15 (46.9)	17 (53.1)	
Gender				
Male	45	23 (51.1)	22 (48.9)	0.286
Female	31	12 (38.7)	19 (61.3)	
Lymph node metastasis				
Absent	20	7 (35.0)	13 (65.0)	0.248
Present	56	28 (50.0)	28 (50.0)	
Site of tumor				
Body or tail	18	14 (77.8)	4 (22.2)	0.002
Head	58	21 (36.2)	37 (63.8)	
Histological type				
Well-/moderate	62	30 (48.4)	32 (51.6)	0.514
Poor	13	5 (38.5)	8 (61.5)	
UICC stage				
II	22	9 (40.9)	13 (59.1)	0.566
III	54	26 (48.1)	28 (51.6)	
Tumor remnant				
R0	55	27 (49.1)	28 (50.9)	0.390
R1	21	8 (38.1)	13 (61.9)	
Portal vein resection				
No	51	28 (54.9)	23 (45.1)	0.027
Yes	25	7 (28.0)	18 (72.0)	
Complications				
No	48	23 (47.9)	25 (52.1)	0.669
Yes	28	12 (42.9)	16 (57.1)	
IBL				
<1,000 ml	44	33 (75.0)	11 (25.0)	<0.001
≥1,000 ml	32	2 (6.2)	30 (93.8)	
Operative time				
<8 h	33	24 (72.7)	9 (27.3)	<0.001
≥8 h	43	9 (25.6)	32 (74.4)	

UICC: Union for International Cancer Control. *Significant effect in this study.

Results

Patients. We evaluated 76 patients (median age=66 years; range=40-84 years; male, n=45; female, n=31) in the present study. The median follow-up period was 14.5

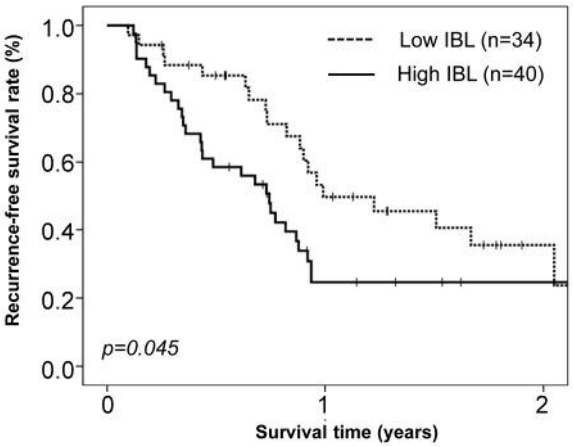

Figure 2. *The recurrence free survival rates in the groups with intraoperative blood loss (IBL) ≥1,000 ml and <1,000 ml. The study population consisted of patients who underwent potentially curative surgery for stage II/III pancreatic cancer (p=0.045).*

months (range=3-65 months). Eighteen patients underwent distal pancreatic surgery and 58 pancreaticoduodenectomy. The median operative time was 493 minutes (range=140-935 min). The median blood loss was 1115 ml (range=140-6340 ml).

Clinicopathological features. IBL of 1,000 ml was considered to be the optimal cutoff point for classification based on ROC curve analyses (area under the curve (AUC)=0.74, 95% confidence interval=0.592-0.829; p=0.002) (Figure 1). Table I summarizes the clinicopathological data of the patients in the groups with low and high IBL. There were significant differences in the distribution of tumor site, the rates of portal vein resection and blood transfusion, and the operative time between the two groups. In the high IBL cases, tumors were more frequently located in the pancreatic head, portal vein resection was performed more frequently and operative time was longer.

Long-term outcomes. The 1- and 2-year RFS rates were 49.8% and 35.5%, respectively, in the group with high IBL, and 24.6% and 24.6% in the low IBL group (p=0.045). The RFS curves are shown in Figure 2.

The prognostic significance of each clinicopathological factor was analyzed (Table II). The univariate analyses of factors associated with OS demonstrated that IBL was a significant prognostic factor. Thus, IBL was included in the final multivariate analysis model. The 5-year OS was 36.6% in the group with IBL<1,000 ml and 11.4% in that with IBL≥1,000 ml, a statistically significant difference (p=0.003). The OS curves are shown in Figure 3.

Discussion

The present study examined whether IBL was associated with poorer OS and RFS in patients who underwent curative surgery for pancreatic cancer. Our findings clearly indicate that IBL was an independent risk factor for both OS and RFS. Thus, IBL had a clinical impact in patients who underwent radical surgery for pancreatic cancer and effective adjuvant chemotherapy.

IBL has been reported to be associated with the prognosis of patients with digestive carcinoma (17-20). Katz *et al*. reported that increased IBL during hepatic resection was an independent prognostic factor for tumor recurrence and death in patients with hepatocellular carcinoma (17). There are two articles on the association between IBL and prognosis in patients with gastric cancer. Liang *et al*. reported IBL to be an independent prognostic factor for patients who had undergone curative for resection gastric cancer. A reduction of IBL can improve the long-term outcomes of patients after curative gastrectomy for gastric cancer (19). Ito *et al*. also reported that IBL adversely influenced the long-term outcomes of patients with stage II/III gastric cancer (20). In pancreatic cancer, Nagai *et al*. reported that IBL was a prognostic determinant of survival after surgery for pancreatic cancer and that operative blood loss enabled stratification of patients by risk of pancreatic cancer mortality (18). On the other hand, there are also studies that whilst emphasizing the importance of minimizing IBL did not find it to be an independent prognostic factor in patients with cancer (21, 22). In our study, survival was independently influenced by IBL in patients who underwent curative surgery for pancreatic cancer.

An important limitation that potentially affects the available data regarding IBL in all studies, including the current study, is the lack of consensus regarding the most appropriate cut-off point for IBL. In previous studies, IBL ranged from 330 ml to 1,000 ml and the population of patients with gastric cancer ranged from 152 to 1,013 (23). For example, Ito *et al*. evaluated the prognostic impact of IBL in 1,013 patients with resected gastric cancer (20). A ROC curve analysis to determine the amount of IBL that best predicted post-operative disease recurrence within 3 years after surgery yielded a cut-off value of 330 ml (hazard ratio=1.40, 95% confidence intervaI=1.03-1.91; p=0.0341). Liang *et al*. evaluated the prognostic impact of IBL in 845 patients who underwent resection of gastric cancer. They set a cut-off value of 200 ml based on the cancer-specific survival (hazard ratio=1.590, 95% confidence intervaI=1.140-2.217; p=0.0001) (19). In our study, the ROC analysis revealed that the optimal cut-off value for predicting OS was 1,000 ml. Nagai *et al*. also evaluated the prognostic impact of IBL in 614 patients with pancreatic cancer. Based on an ROC curve analysis to determine the

Table II. *Univariate and Multivariate Cox proportional hazards analysis of clinicopathological factors for overall survival.*

Factor Value	Subgroup	No	Univariate analysis			Multivariate analysis			-
			OR	95% CI	*p*-Value	OR	95% CI	*p*	
Age	<70 Years	44	1.000		0.365				
	≥70 Years	32	1.333	0.716-2.480					
Gender	Male	45	1.000		0.085				
	Female	31	1.731	0.927-3.230					
Lymph node metastasis	Absent	20	1.000		0.971				
	Present	56	0.987	0.491-1.985					
Site of tumor	Body or tail	18	1.000		0.157				
	Head	58	1.875	0.784-4.480					
Histological type	Well-/moderate	62	1.000		0.119				
	Poor	13	1.770	0.863-3.629					
UICC stage	II	22	1.000		0.546				
	III	54	1.240	0.618-2.488					
Tumor remnant	R0	55	1.000		0.041	1.000		0.039	
	R1	21	1.764	1.029-3.676		1.959	1.034-3.711		
Complications	No	48	1.000		0.267				
	Yes	28	1.434	0.759-2.710					
IBL	<1,000 ml	44	1.000		0.004	1.000		0.017	
	≥1,000 ml	32	2.754	1.388-5.463		2.391	1.166-4.903		
Operative time	<8 h	33	1.000		0.032	1.000		0.162	
	≥8 h	43	2.212	1.072-4.564		1.706	0.808-3.602		

CI: Confidence intervaI; HR: hazard ratio: IBL: intraoperative blood loss; UICC: Union for International Cancer Control.

threshold values of IBL that predicted mortality, they stratified patients into three groups: <1,000 ml, 1,000-2,000 ml, and >2,000 ml; IBL >2,000 ml remained an independent prognostic factor in a multivariate analysis (hazard ratio=2.55; *p*=0.003) (18). There are some differences between the present study and previous studies because of their different sample sizes.

In this study, portal vein resection was more frequently performed in the group with high IBL, and IBL and residual tumor were included as factors in the final multivariate analysis model to identify prognostic factors. Portal resection and plexus dissection are actively performed at our Institution to achieve curative resection. These results indicate that the negative effect of excessive blood loss and the aggressiveness of residual tumor may independently affect the prognosis. Thus, reducing blood loss in patients with borderline resectable pancreatic cancer with portal vein invasion might further improve their survival.

Our findings have some clinical limitations. Firstly, it was a retrospective study with a relatively small sample size; a large-scale prospective validation study is needed. Secondly, there was a selection bias in the patients in this series. Surgeons avoid performing pancreatectomy in some patients because of high rates of morbidity and mortality associated with this operative method. Thus, the fact that some patients in this study underwent pancreatectomy might in and of itself be considered a potential bias. Thirdly, the present study did not use an optimal cut-off value for the IBL.

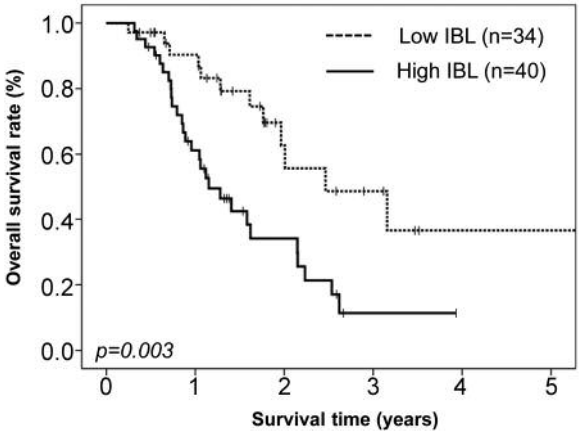

Figure 3. *The overall survival rates in the groups with intraoperative blood loss (IBL) ≥1,000 ml and <1,000 ml. The study population consisted of patients who underwent potentially curative surgery for stage II/III pancreatic cancer (p=0.003).*

In conclusion, the OS and RFS of patients with stage II/III pancreatic cancer who underwent curative resection differed significantly based on the amount of IBL. The results of the

present study suggest that reducing IBL may improve the prognosis of patients with stage II/III pancreatic cancer.

Conflicts of Interest

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

Authors' Contributions

HT and TA made substantial contributions to conception and design. NY, MK, MM (Masaaki Murakawa), YA, MN, KK, MM (Munetaka Masuda), KH, NY, YR and SM made substantial contributions to acquisition of data, or analysis and interpretation of data. TA, KK, HT and YR were involved in drafting the article or revising it critically for important intellectual content. MN, KK, KH, and NY gave final approval of the version to be published. Each Author participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All Authors read and approved the final article.

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