Adverse impact of postoperative intra-abdominal infectious complications on cancer recurrence-related survival after curative gastric cancer surgery

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Abstract

Background: This study aimed to evaluate the impact of postoperative intra-abdominal infectious complications (PICs) on survival after surgery for gastric cancer.

Methods: A total of 152 patients who underwent curative gastrectomy for gastric cancer were included. The effect of clinicopathological features and PICs on recurrence-free survival (RFS) and overall survival (OS) were investigated.

Results: The median age was 67 years. The pathological stage was stage I (61), II (40), and III (51). Thirty-two patients (21.1%) had PICs: 9, pancreatic fistula; 14, anastomotic leakage; and 17, intra-abdominal abscess. The five-year RFS and OS rates were significantly lower in patients with PICs than in those without PICs (63.4 vs. 85.6%; $p < 0.01$ and 56.4 vs. 80.3%; $p < 0.01$, respectively). In multivariate analysis, intraoperative blood loss was an independent prognostic factor for PICs.

Conclusions: Patients with PICs had worse clinical outcomes. Reducing intraoperative bleeding may improve the prognosis of gastric cancer.

Keywords: gastric cancer, postoperative intra-abdominal infectious complications, intraoperative bleeding, postoperative complication

INTRODUCTION

Gastrectomy with lymph node dissection (LND) is the preferred curative treatment option for patients with gastric cancer,[1] and postoperative adjuvant chemotherapy improves survival.[2] However, a significant number of patients suffer from recurrence, particularly after surgery for advanced gastric cancer, even after R0 resection.[3–5] Gastrectomy with D2 LND has been accepted as the standard treatment for advanced gastric cancer.[1,6,7] However, Western randomized trials have failed to provide sufficient evidence on the efficacy of D2 LND, presumably because of the increased incidence of postoperative morbidity. In particular, this result is thought to be attributed to an increase in early in-hospital deaths after D2 LND.[8–10] Another possible reason is that postoperative complications could have increased the incidence of deaths following cancer recurrence.

Recently, postoperative morbidity has been reported to have adverse effects on long-term as well as short-term outcomes in several tumors.[11] In colorectal cancer, anastomotic leakage is generally associated with a high rate of local recurrence and a poor long-term survival rate.[12–14] In gastric cancer, patients with postoperative intra-abdominal infectious complications (PICs) may follow a severe clinical course. Moreover, PICs may adversely affect both long-term and short-term outcomes. Tokunaga et al.[11] reported that PICs were strongly associated with poor overall survival (OS) and recurrence-free survival (RFS). Surgical trauma can impair tissue integrity and activate inflammatory mediators and angiogenic factors.[15] However, it

remains unclear whether complications or inflammation that occurs early after gastric cancer surgery is associated with long-term cancer recurrence and prognosis.

This study aimed to evaluate the long-term prognosis in patients with PICs after curative gastric cancer surgery.

MATERIALS AND METHODS

Patients and study approval

We investigated 152 consecutive patients with gastric cancer who underwent curative surgery for LND between January 2014 and December 2017 at the Department of Gastrointestinal Surgery, Shiga University of Medical Science Hospital, Japan. Tumor stage and pathological classification were described according to the *Japanese Classification of Gastric Carcinoma*.[16]

The study protocol was approved by the Ethics Committee of Shiga University of Medical Science and was in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all patients.

Postoperative intra-abdominal infectious complications

In this study, the Clavien–Dindo (CD) classification was used to classify postoperative intra-abdominal complications in each patient.[17,18] According to the CD classification, patients were classified as having grade II complications if antibiotics were administered and grade IIIa or IIIb if surgical intervention was indicated. If patients required admission to the intensive care unit, they were regarded as having grade IVa or IVb complications. Postoperative mortality was considered as a grade V complication. If multiple complications occurred in a single patient, the highest grade was used. A PIC was defined as pancreatic fistula, anastomotic leakage, or intra-abdominal abscess, and classified as grade II or higher.

Postoperative clinical outcomes

Independent prognostic factors were identified using the Cox proportional hazards model. In the analysis, age, sex, tumor invasion, lymph node metastasis, histological type, pathological stage, operation time, intraoperative blood loss, PIC, and postoperative complications other than PIC were included as covariates. Independent risk factors for PICs were identified using logistic regression analysis wherein age, sex, tumor invasion, lymph node metastasis, LND, operation time, and intraoperative blood loss were included as covariates.

Survival

Based on the PIC results, patients were divided into two groups: the PIC group and the non-PIC group. RFS and OS were analyzed using the Kaplan–Meier method. OS and RFS were calculated from the date of initial surgery to the date of death or a clinical diagnosis of recurrence, respectively. Differences between the survival curves were analyzed using the generalized log-rank test.

Statistical analyses

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R software (The R Foundation for Statistical Computing, version 2.13.0, Vienna, Austria).[19] Independent factors that appeared to be significant in the univariate analysis were subsequently assessed using multivariate analysis. Confidence intervals (CIs) were determined at a 95% level. Statistical significance was set at $p < 0.05$.

RESULTS

Patient characteristics and PICs

This study evaluated 152 patients who underwent curative gastrectomy with LND. Clinical characteristics of the patients are presented in Table 1. Of the 152 patients, 32 (21.1%) were found to have the following PICs: 9 with pancreatic fistula, 14 with anastomotic leakage, and 17 with intra-abdominal abscess (including overlap cases). Among the patients who underwent D2 lymph node dissection, 24 were found to have the following PICs: eight with pancreatic fistula (8.8%), eight with anastomotic leakage (8.8%), and 16 with intra-abdominal abscess (17.6%). Postoperative complications other than PIC were also identified: two patients with pulmonary embolism, five with pneumonia, two with intestinal obstruction, five with renal dysfunction, and one with postoperative bleeding.

Among those diagnosed with stages II and III, 72 patients received adjuvant chemotherapy (AC). Of 32 patients in the PIC group, 24 patients were indicated for AC, and 20 patients received AC (83.3%). Of 120 patients in the non-PIC group, 67 patients were indicated for AC, and 52 patients received AC (77.6%). There was no difference in the number of patients receiving AC ($p = 0.55$). In addition, the completion rate of AC was 95% and 92.3% in the PIC group and non-PIC group, respectively ($p = 0.68$).

PICs as a prognostic factor

Postoperative RFS and OS were analyzed using the Cox proportional hazards model, which showed that PIC was an independent prognostic factor (RFS: hazard ratio, 2.51; 95% CI, 1.14–5.51; $p = 0.046$; OS: hazard ratio, 2.746; 95% CI, 1.15–5.31; $p = 0.019$) (Table 2). Complications other than PICs were not significantly associated with survival. In addition, AC was also not significantly correlated with patient survival.

Risk factor for PICs

We evaluated the risk factors for PICs. As shown in Table 3, multivariate analysis using logistic regression identified intraoperative blood loss as an independent risk factor for PICs (odds ratio, 2.61; 95% CI, 1.09–5.49; $p = 0.043$).

PICs and clinical outcomes

We also assessed the correlation between PICs and clinical outcomes. Table 4 shows the details of subgroup analysis of 32 patients in the PIC group and 120 in the non-PIC group. Pathological tumor invasion, pathological stage, D2 LND, operation time, and intraoperative blood loss were significantly higher in the PIC group than in the non-PIC group ($p < 0.05$). Figure 1 shows the RFS and OS in both groups. The five-year RFS and OS rates were 63.4 and 56.4% in the PIC group and 85.6 and 80.3% in the non-PIC group, respectively. The RFS and OS in the PIC group were significantly lower than those in the non-PIC group ($p < 0.01$ in both cases).

Intra-abdominal surgery, percutaneous drainage, or antibiotics alone were the treatments provided when PICs were detected. The anastomotic leaks were managed as follows: four patients with intra-abdominal surgery, six patients with percutaneous drainage, and four patients with antibiotics alone. The pancreatic fistulas were managed as follows: five patients with percutaneous drainage and four patients with antibiotics alone. The intra-abdominal abscesses were managed as follows: nine patients with percutaneous drainage and eight patients with antibiotics alone. The RFS was 24.5% and 70.1% in CD grade III and grade II, respectively ($p = 0.041$). The OS was 29.1% and 75% in CD grade III and grade II, respectively ($p = 0.075$). The patients who required drainage or surgery had poor survival outcomes.

These findings indicate that patients with PICs have worse clinical outcomes. Prevention of PICs can contribute to better clinical outcomes.

DISCUSSION

The findings of this study showed that PICs had a significant impact on RFS and OS in patients with gastric cancer who underwent curative gastrectomy. Therefore, prophylaxis for PICs is important to improve clinical outcomes.

For patients with gastric cancer, gastrectomy with LND is the preferred curative treatment option, and perioperative AC generally improves survival.[1,2,20] However, surgery inevitably results in several postoperative complications. Despite the best efforts of gastrointestinal surgeons and the advancements in surgical technology, the incidence of postoperative complications has been reported to range from 20 to 35%.[21–24]

Several reports have shown a strong correlation between postoperative complications and poor long-term outcomes in gastric cancer. In a study by Tokunaga et al.,[11] which only included patients who underwent surgery before 2006 to eliminate the effects of perioperative chemotherapies, it was found that PICs adversely affected OS and RFS. This indicates that PICs has an impact on prognosis regardless of chemotherapy. Yu et al.[24] reported that not only PICs but also other postoperative complications, including pneumonia, urinary tract infection, and non-infectious complications, had a significant negative impact on long-term survival. In contrast, in the current study, PICs were significantly associated with RFS and OS, while postoperative complications other than PICs were not associated with prognosis. Although the relationship between non-PIC complications and prognosis is not fully understood, our findings are consistent with previous results suggesting that intra-abdominal complications accompanied by infection increase the risk of cancer recurrence and affect survival. In addition, intraoperative blood loss was identified as an independent risk factor for the development of PICs. Thus, efforts to reduce bleeding, such as attempting a less invasive surgery and/or careful hemostasis, can reduce early postoperative complications and improve the long-term prognosis

of cancer. However, the correlation between blood loss and PICs is unclear. Blood loss is considered to cause not only local damage, but also systematic change and organ ischemia. The loss of wound healing factors (glutamine and arginine) by blood loss may lead to postoperative complications. In the future, further study is required to show the correlation between blood loss and PICs.

It remains unclear how exactly PICs affect the long-term outcomes in patients. In previous works, we have shown that viable cancer cells spill into the peritoneal cavity during curative gastric cancer surgery, in which cancer cells are associated with recurrence.[15,25,26] Generally, a single free cancer cell easily undergoes apoptosis *in vivo*, and immunological defenses may eliminate most of the disseminated tumor cells. However, various metastatic factors induced by surgery have been recently proposed.[27,28] Surgical trauma impairs tissue integrity and induces the activity of inflammatory mediators and angiogenic factors, leading to immune suppression, enhanced tumor cell adhesion, and augmented tumor growth. In addition, PICs may accelerate these local and systemic changes. Thus, environmental changes surrounding cancer cells caused by PICs may contribute to the recurrence of cancer cells present in the abdominal cavity after surgery.

Furthermore, the incidence of PICs may also delay the initiation of chemotherapy. If the patient physical status and postoperative recovery are appropriate, AC should be recommended in a timely manner for those at a high risk of recurrence. The administration of perioperative chemotherapies has been accepted because it increases the survival rate of patients with advanced gastric cancer.[2,29-31] Tokunaga et al.[11] reported that PICs adversely affected the OS and RFS by hindering the administration of AC in patients. This suggests that PICs themselves affect clinical outcomes. Lu et al.[32] reported that every four-week delay in the initiation of AC was associated with worse survival outcomes. However, Greenleaf et al.[33] reported that the time to the initiation of AC did not affect survival. The relationship between the delay in AC

initiation due to the onset of PICs and survival time thus requires further investigation.

Some limitations to consider when interpreting the findings of the current study include the relatively small sample size and the single-center retrospective design. Nonetheless, there was a significant prognostic difference established between the PICs and non-PICs groups. In the future, the relationship between PICs and recurrence should be investigated in a multicenter large-scale study. In addition, the mechanism by which PICs induce recurrence should be elucidated in terms of delayed initiation of chemotherapy and changes in the microenvironment of intraperitoneal cancer cells.

The efforts to reduce early postoperative complications are necessary to improve the long-term prognosis of cancer. Ida et al. reported that the cause of pancreatic leakage can be compression by the assistant's forceps.[34] Therefore, standardization of the surgical procedure is required to reduce postoperative complications. The use of several other techniques, devices, and nutritional support may help prevent these complications.

CONCLUSIONS

This study confirmed that PICs in patients after gastric cancer surgery were associated with poor RFS and OS. Patients with PICs had worse clinical outcomes. Surgery aimed to reduce bleeding, which is an independent risk factor for PIC, may not only reduce postoperative complications but also contribute to improving the overall prognosis. It is necessary to elucidate the mechanism by which PICs lead to postoperative recurrence of cancer and to establish a therapeutic strategy to prevent the development of PICs.

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List of abbreviations

PIC: postoperative intra-abdominal infectious complication

RFS: recurrence-free survival

OS: overall survival

LND: lymph node dissection

CD: Clavien–Dindo

AC: adjuvant chemotherapy

CI: confidence intervals

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Figure legends

Figure 1. Recurrence-free survival and overall survival after curative surgery for gastric cancer. The curves are plotted using the Kaplan-Meier method and analyzed using the log-rank test. Survival curves are separated according to postoperative intra-abdominal infectious complication.

357 **Tables**

358 **Table 1.** Characteristics of gastric cancer patients (n=152)

359 **Table 2.** Univariate and multivariate analysis of evaluable factors in recurrence-free survival
360 and overall survival

361 **Table 3.** Univariate and multivariate analysis of risk factors on postoperative intra-abdominal
362 infectious complication

363 **Table 4.** Comparison of clinicopathological factor selected accordingly to postoperative intra-
364 abdominal complication

365

Table 1 Characteristics of patients who underwent gastrectomy and lymph node dissection

Patients with gastric cancer (n = 152)	
Age (median, range) (years)	67 (35–93)
Sex	
Male / Female	112 / 40
Pathological tumor invasion	
m / sm / mp / ss / se	22 / 33 / 26 / 29 / 42
Pathological lymph node metastasis	
0 / 1 / 2 / 3	78 / 21 / 28 / 25
Pathological stage	
I / II / III	61 / 40 / 51
Cytology	
negative / positive	152 / 0
Histological type	
Differentiated / Undifferentiated	87 / 65
Surgery	
Distal gastrectomy / Total gastrectomy	102 / 50
Operation time	
median (range) (min)	425 (175-768)
Intraoperative blood loss	
median (range) (min)	610 (15-2254)
PICs	32*
pancreatic fistula	9
anastomotic leakage	14
intra-abdominal abscess	17
postoperative complications other than PIC	
pulmonary embolism	2
pneumonia	5
intestinal obstruction	2
renal dysfunction	5
postoperative bleeding	1
Adjuvant chmetherapy (Stage II and III)	91
Yes	72
No	19

m, mucosa; sm, submucosa; mp, muscularis propria; ss, subserosa; se, serosa-exposed.

PICs, postoperative intra-abdominal infectious complications; *, including overlap cases

Table 2 Multivariate analysis of evaluable factors in recurrence free survival and overall survival

Recurrence free survival

Factors	HR	95%CI	Univariate analysis	HR	95%CI	Multivariate analysis
age (>70)	1.478	0.70-3.11	0.3			
Sex (Male)	1.254	0.53-2.95	0.6			
Pathological tumor invasion (T2-4)	17.26	2.34-127.1	0.005	1.821	0.16-20.25	0.625
Pathological lymph node metastasis	10.41	3.13-34.5	<0.001	2.366	0.46-12.13	0.302
Pathological stage (II, III)	15.55	4.68-51.62	<0.001	4.26	0.68-26.51	0.12
Histological type	1.761	0.83-3.72	0.138			
Operation time (>480min)	1.898	0.90-3.98	0.090			
Intraopeative blood loss (>500ml)	2.194	0.96-4.99	0.060			
PIC	3.007	1.4-6.43	0.004	2.51	1.14-5.51	0.021
postoperative complications other than PIC	0.614	0.18-2.01	0.422			
adjuvant chemotherapy* (No)	0.838	0.31-2.19	0.71			

Overall survival

Factors	HR	95%CI	Univariate analysis	HR	95%CI	Multivariate analysis
age (>70)	3.592	1.74-7.39	<0.001	4.214	1.95-9.08	<0.001
Sex (Male)	2.645	1.01-6.87	0.045	3.625	1.36-9.60	0.009
Pathological tumor invasion (T2-4)	4.913	1.73-13.9	0.002	1.342	0.33-5.42	0.679
Pathological lymph node metastasis	3.94	1.79-8.78	<0.001	1.278	0.32-5.0	0.726
Pathological stage (II, III)	6.007	2.71-13.3	<0.001	3.877	0.79-19.02	0.094
Histological type	0.774	0.38-1.54	0.464			
Operation time (>480min)	0.9651	0.47-1.95	0.92			
Intraopeative blood loss (>500ml)	1.672	0.82-3.38	0.152			
PIC	2.615	1.28-5.3	0.007	2.476	1.15-5.31	0.019
postoperative complications other than PIC	0.671	0.20-2.20	0.511			
adjuvant chemotherapy* (No)	1.17	0.47-2.88	0.73			

HR, Hazard ratio; CI, confidence interval; PIC, postoperative intra-abdominal infectious complication;

*, only stage II and III

Table 3 Multivariate analysis of risk factors on postoperative intra-abdominal infectious complication

Factors	Odds	95%CI	Univariate analysis	Odds	95%CI	Multivariate analysis
age (>70)	1.12	0.51-2.44	0.78			
Sex (Male)	1.78	0.67-4.71	0.243			
Pathological tumor invasion (T2-4)	3.73	1.34-10.3	0.011	2.45	0.70-8.53	0.16
Pathological Lymph node metastasis	1.97	0.88-4.39	0.097			
D2 lymph node dissection	2.98	1.33-6.69	0.007	1.59	0.57-4.35	0.37
Surgery (total gastrectomy)	1.88	0.76-3.39	0.10			
Operation time (>480min)	1.37	0.61-3.05	0.443			
Intraopeative blood loss (>500ml)	2.71	1.13-6.52	0.025	2.61	1.09-5.49	0.043

CI, confidence interval; PIC, postoperative intra-abdominal infectious complication

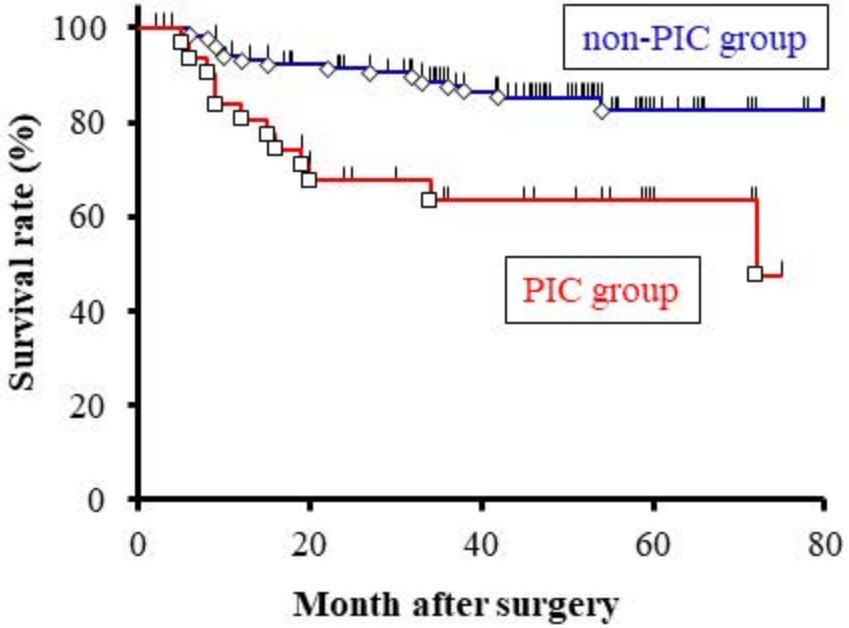
Table 4. Comparison of clinicopathological factor accordingly to postoperative intra-abdominal complication

	Gastric cancer patients (n =152)		
	PIC group (n = 32)	**Non- PIC group** (n=120)	p value
Age (median, range) (years)	70 (48-84)	68 (35-93)	0.69
Sex			
Male / Female	26 / 6	86 / 34	0.29
Hemoglobin (median, range) (g/dL)	12.3 (9.5-14.4)	12.1 (9.9- 13.9)	0.78
Albumin (median, range) (g/dL)	3.8 (3.5-4.0)	3.8 (3.4-4.4)	0.81
Pathological tumor invasion	5 / 27	50 / 70	<0.01
m, sm / mp, ss, se			
Pathological lymph node metastasis	12 / 6 / 7 / 7	66 / 15 / 21 / 18	0.078
0 / 1 / 2 / 3			
Pathological stage	8 / 6 / 18	53 / 34 / 33	0.035
I / II / III			
Histological type	16 / 16	71 / 49	0.35
Differentiated / Undifferentiated			
Surgery	18 / 14	84 / 36	0.14
Distal gastrectomy / Total gastrectomy			
Lymph node dissection	8 / 24	53 / 67	0.049
D1 / D2			
Splenectomy	2 / 30	4 / 116	0.45
yes / no			
Operation time (median, range) (min)	456 (297-768)	372 (175-692)	<0.01
Intraoperative blood loss (median, range) (min)	850 (20-2254)	516 (15-2220)	<0.01
Perioperative transfusion	14	24	<0.01
yes / no			

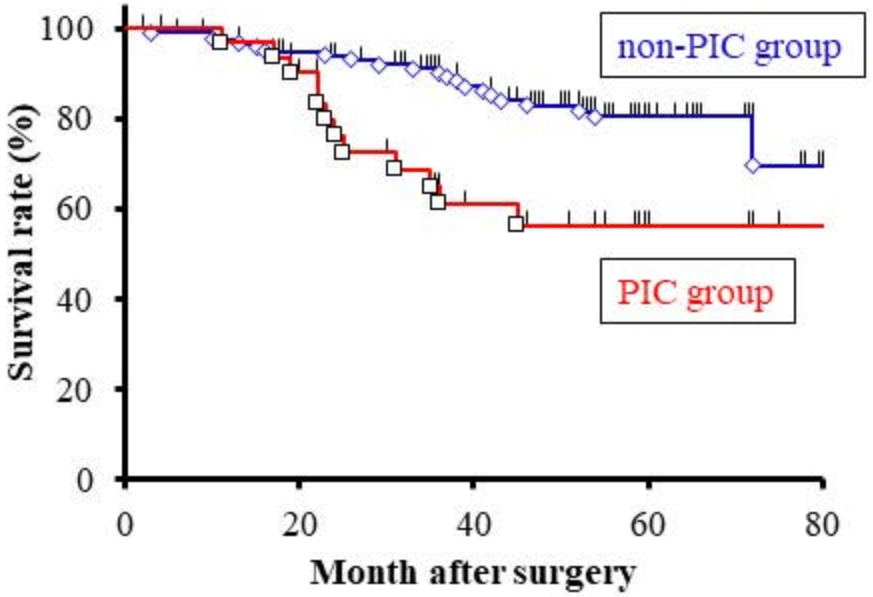
PIC, postoperative intra-abdominal infectious complication;
m, mucosa; sm, submucosa; mp, muscularis propria; ss, subserosa; se, serosa-exposed.

Fig. 1 Recurrence-free survival and overall survival using the Kaplan-Meier method

RFS



OS



5-year RFS (%)

PIC group 63.4% vs non-PIC group 85.6%

$p < 0.01$

5-year OS (%)

PIC group 56.4% vs non-PIC group 80.3%

$p < 0.01$