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Differences Between Laparoscopic and Open Gastrectomy on the Impact of Postoperative Infectious Complications on Prognosis

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Abstract. *Background/Aim: The aim of this study was to evaluate the impact of laparoscopic gastrectomy (LG) for gastric cancer on long-term survival in patients with postoperative infectious complications (PIC). Patients and Methods: A total of 608 patients who underwent gastrectomy were classified into two groups based on the surgical approach: LG (385 patients) and open gastrectomy (OG: 211 patients). Long-term survival after gastrectomy was compared between patients with and without PIC in both LG and OG groups. Results: Although the patients with PIC in OG group tended to have worse overall survival (OS) than those without PIC, the OS was not significantly different between the patients with and without PIC in LG group. Although multivariate analysis demonstrated that nodal involvement and PIC were significantly associated with OS in OG group, age and tumor depth, and not PIC, were associated with OS in LG group. Conclusion: PIC were negative predictors of clinical outcomes in patients with gastric cancer, particularly those who underwent OG, and long-term prognosis may be impacted less by PIC in patients undergoing LG.*

Albeit considerable advances in prevention, diagnosis, and therapy for postoperative infections, morbidity rates following gastrectomy with D2 lymphadenectomy range between 19.6% and 26.2% worldwide (1, 2). Postoperative infectious complications (PIC) increase the cost of treatment, delay adequate adjuvant therapy, affect quality of life, and may be associated with poor prognosis (3, 4). In addition, increasing evidence suggest that PIC are significantly associated with negative long-term outcomes in various malignancies (5-10).

Minimal invasive surgery for gastrointestinal cancers has recently become prevalent. The noninferiority of laparoscopic gastrectomy (LG) over conventional open gastrectomy (OG) for long-term outcomes has been reported previously (11). We recently demonstrated that less invasive surgery was associated with reduced postoperative inflammatory responses compared to conventional open surgery (12, 13). However, none of the studies to date have assessed the surgical invasiveness of gastrectomy on the poor long-term survival associated with PIC in gastric cancer.

We hypothesized that the difference in surgical approach had a distinct effect on long-term outcomes in patients with PIC. However, it is apparent that LG may be performed at an earlier stage of gastric cancer as compared with conventional OG. To that end, we investigated the impact of differences in surgical approaches for gastrectomy on long-term outcomes after a potentially curative resection for gastric cancer in patients with PIC according to the stage of disease.

Patients and Methods

Patients. Between 2009 and 2016, 787 consecutive patients underwent gastrectomy for adenocarcinoma of the stomach at National Defense Medical College Hospital (Tokorozawa, Saitama, Japan). Among these, 596 patients (455 males, 141 females; mean age, 69.0±0.4 years; range=32-92 years) who underwent gastrectomy with potentially curative resection were included in the current study. Two hundred eleven patients underwent open gastrectomy and 365 patients underwent laparoscopic gastrectomy. We excluded patients who underwent R1 or R2 surgery, those who underwent pancreatosplenectomy, those who underwent gastrectomy for benign diseases or gastrointestinal stromal tumors, those who received preoperative chemotherapy, those with in-hospital mortality, and those with an observation period of 100 days or less. The resected specimens were examined histopathologically and staged according to the third English edition of the Japanese

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Key Words: Minimal invasive surgery, gastric cancer, postoperative infectious complications, surgical stress, prognosis.

Table I. *Demographic and clinicopathological data of patients who underwent open gastrectomy or laparoscopic gastrectomy.*

	All patients (n=596)				
	OG		LG		
	(n=211)	%	(n=385)	%	p-Value
Age (median, range)	71 (36-92)		70 (32-89)		0.09
Gender (M:F)	168:43		287:98		0.16
Body mass index (median, range)	22.0 (16.0-34.7)		22.5 (14.3-38.7)		0.11
Tumor size (mm) (median, range)	59 (8-215)		33 (1-150)		<0.01
Location					
U	70	33%	83	21%	<0.01
M	63	30%	130	34%	
L	78	37%	172	45%	
Tumor depth					
T1	40	19%	253	66%	<0.01
T2	30	14%	53	14%	
T3	75	36%	54	14%	
T4	66	31%	25	6%	
Nodal involvement					
N0	68	32%	291	76%	<0.01
N1	48	23%	49	13%	
N2	39	18%	24	6%	
N3	56	27%	21	5%	
Stage					
I	50	24%	276	72%	<0.01
II	59	28%	72	19%	
III	97	46%	35	9%	
IV	5	2%	2	1%	
Surgical procedure					
Distal gastrectomy	105	50%	210	55%	<0.01
Proximal gastrectomy	5	2%	31	8%	
PPG	3	1%	62	16%	
Total gastrectomy	98	46%	82	21%	
Extent of lymphadenectomy					
D0	5	2%	2	1%	<0.01
D1	39	18%	237	62%	
D2	167	79%	146	38%	
Resection of other organs					
Yes	79	37%	33	9%	<0.01
No	132	63%	352	91%	
Operating time (median, range) (minutes)	233 (82-474)		250 (123-548)		<0.01
Blood loss (ml)	415 (10-6,063)		44 (0-3,110)		<0.01
Blood transfusion					
Yes	44	21%	13	3%	<0.01
No	167	79%	372	97%	
Postoperative hospital stay (days)	13 (6-820)		9 (5-2,202)		<0.01
Postoperative infectious complication					
Yes	67	32%	62	16%	<0.01
No	144	68%	323	84%	

OG: Open gastrectomy; LG: laparoscopic gastrectomy; U: upper third of the stomach; M: middle third of the stomach; L: lower third of the stomach; PPG: pylorus-preserving gastrectomy.

Classification of Gastric Carcinoma (14). Adjuvant chemotherapy with oral anti-cancer agents such as fluoropyrimidine (S-1), was recommended in patients with stage II or III gastric cancer. Seven patients in the study cohort had early gastric cancer with incomplete D1 lymphadenectomy (D0) with sentinel node navigation surgery, which was a potentially curative resection. These patients were retrospectively evaluated for their pre- and post-operative status, pathological findings, and surgical procedures based on the data in the electronic records or medical and nursing charts.

This is a non-randomized, retrospective and single institutional study. LG has been introduced since 2007, and the indication of LG was a tumor depth of cT2 or less regardless of any lymph node

Table II. *Demographic and clinicopathological characteristics of patients with or without postoperative infectious complications who underwent open gastrectomy or laparoscopic gastrectomy.*

	With PIC					Without PIC				
	OG (n=67)	%	LG (n=62)	%	*p*-Value	OG (n=144)	%	LG (n=323)	%	*p*-Value
Age (median, range)	73 (50-86)		72.5 (39-88)		0.73	71 (36-92)		70 (32-89)		0.23
Gender (M:F)	54:13		48:14		0.66	114:30		239:84		0.23
Body mass index	22.6 (16.2-34.7)		23.0 (17.2-32.9)		0.79	21.9 (16.0-30.9)		22.4 (14.3-38.7)		0.04
Tumor size (mm)	67 (14-215)		36.5 (2-137)		<0.01	55 (8-190)		32 (1-150)		<0.01
Location										
U	28	42%	15	24%	0.18	42	29%	68	21%	0.01
M	18	27%	24	39%		45	31%	106	33%	
L	21	31%	23	37%		57	40%	149	46%	
Tumor depth										
T1	15	22%	36	58%	<0.01	25	17%	217	67%	<0.01
T2	5	7%	10	16%		25	17%	43	13%	
T3	26	39%	10	16%		49	34%	44	14%	
T4	21	31%	6	10%		45	31%	19	6%	
Nodal involvement										
N0	21	31%	41	66%	<0.01	47	33%	250	77%	<0.01
N1	20	30%	10	16%		28	19%	39	12%	
N2	8	12%	4	6%		31	22%	20	6%	
N3	18	27%	7	11%		38	26%	14	4%	
Stage										
I	16	24%	36	58%	<0.01	34	24%	240	74%	<0.01
II	18	27%	18	29%		41	28%	54	17%	
III	31	46%	8	13%		66	46%	27	8%	
IV	2	3%	0	0%		3	2%	2	1%	
Surgical procedure										
Distal gastrectomy	29	43%	30	48%	<0.01	76	53%	180	56%	<0.01
Proximal gastrectomy	0	0%	5	8%		5	3%	26	8%	
PPG	1	1%	8	13%		2	1%	54	17%	
Total gastrectomy	37	55%	19	31%		61	42%	63	20%	
Extent of lymphadenectomy										
D0	2	3%	0	0%	<0.01	3	2%	2	1%	<0.01
D1	10	15%	37	60%		29	20%	200	62%	
D2	55	82%	25	40%		112	78%	121	37%	
Resection of other organs										
Yes	32	48%	6	10%	<0.01	47	33%	27	8%	<0.01
No	35	52%	56	90%		97	67%	296	92%	
Operating time (median, range) (minutes)	243 (88-469)		268 (158-548)		0.20	225 (82-474)		247 (123-492)		<0.01
Blood loss (ml)	513 (52-3,454)		59 (0-3,110)		<0.01	346 (10-6,063)		43 (0-1,655)		<0.01
Blood transfusion										
Yes	22	33%	1	2%	<0.01	22	15%	12	4%	<0.01
No	45	67%	61	98%		122	85%	311	96%	
Postoperative hospital stay (days)	28 (9-820)		20 (6-146)		0.07	11 (6-111)		9 (5-2,202)		<0.01

PIC: Postoperative infectious complications; OG: open gastrectomy; LG: laparoscopic gastrectomy; U: upper third of the stomach; M: middle third of the stomach; L: lower third of the stomach; PPG: pylorus-preserving gastrectomy.

metastasis until 2010, which was expanded in 2011 to a tumor depth of cT4a regardless of any lymph node metastasis.

All procedures were in accordance with the Helsinki Declaration of 1964 and later versions. The study protocol was approved by the Institutional Review Board of the National Defense Medical College. Written informed consent was obtained from every patient before the procedures.

Definition of infectious complications. Complications due to postoperative infections were defined based on the combination of clinical findings and results of laboratory and other tests recorded in the medical records. Clinical evidence was derived from direct observation of the infection site or from review of the patient's chart. Laboratory evidence included culture results, antigen or antibody detection tests, and analysis by microscopic visualization. Supportive

Table III. *Type and frequencies of postoperative infectious complications.*

Infectious complications	All patients (n=596)				
	OG (n=211)	%	LG (n=385)	%	*p*-Value
Pancreatic fistula	21	10%	14	4%	<0.01
Anastomotic leakage	19	9%	18	5%	0.04
Pneumonia	10	5%	17	4%	0.86
Intraperitoneal abscess	7	3%	7	2%	0.25
Enterocolitis	4	2%	3	1%	0.23
Urinary tract infection	3	1%	5	1%	0.90
Cholecystitis	3	1%	4	1%	0.68
Others	2	1%	1	0%	0.26
Total	69	33%	63	16%	<0.01

PIC: Postoperative infectious complications; OG: open gastrectomy; LG: laparoscopic gastrectomy.

Table IV. *Main recurrence site in patients with or without postoperative infectious complications.*

Main recurrence site	With PIC					Without PIC				
	OG (n=67)	%	LG (n=62)	%	*p*-Value	OG (n=144)	%	LG (n=323)	%	*p*-Value
Peritoneal dissemination	8	12%	2	3%	0.10	12	8%	7	2%	0.10
Lymph node metastasis	7	11%	3	5%		8	6%	5	2%	
Liver metastasis	8	12%	1	2%		7	5%	8	2%	
Bone metastasis	0	0%	1	2%		4	3%	1	0%	
Lung metastasis	1	2%	1	2%		3	2%	2	1%	
Local recurrence	1	2%	0	0%		2	1%	4	1%	
Total	25		8			36		27		

PIC: Postoperative infectious complications; OG: open gastrectomy; LG: laparoscopic gastrectomy.

data were derived from other diagnostic studies, such as X-ray, ultrasonography (US), and computed tomography (CT). In the present study, PIC included pneumonia (pyrexia with infiltrates on chest X-ray), enterocolitis (pyrexia with diarrhea and microbiological evidence), cholecystitis (pyrexia with wall thickness diagnosed by US or CT), anastomotic leakage (identified radiographically or clinical suspicion), urinary tract infection (pyrexia with positive culture results) and intraperitoneal abscess, such as pancreatic fistula and other systemic infections (pyrexia with fluid collection diagnosed by US or CT or identified radiographically). Other included infections were central venous catheter-related infections and sepsis. Superficial wound infections were excluded from the study analysis because of their minimal effect on the systemic immune response. In this study, PIC were included if more than grade 3 based on Clavien-Dindo classification (15).

Follow-up. Overall survival (OS) was based on the time interval from the date of resection to the date of death due to any cause. Relapse-free survival (RFS) was based on the time interval from the date of resection to the date of first recurrence or death. Patients who survived were censored in the survival analyses. All patients were observed at the study hospital or the outpatient clinic at 3-4-month intervals during the first two years of the study and every 6 or 12 months thereafter for three years. After 5 years, annual follow-up was performed via telephone conversations with the patient, patient's family, or their practitioner.

Statistical analysis. Statistical analyses were performed using JMP Pro 14.0.0 (SAS Institute, Cary, NC, USA). Data were expressed as means±standard error of the mean. Statistical analyses were performed using either the Mann-Whitney U test or the chi-square test with Fisher's exact test, as appropriate. Survival rates were determined using the Kaplan–Meier method, and the significance of differences in survival rate was determined by the log-rank test. *p*-Values <0.05 were considered statistically significant.

Results

The demographic and clinicopathological data of the study cohort are shown in Table I. The tumor sizes were larger, upper stomach was the most frequent tumor location, and tumor invasion was deeper in the patients who underwent OG compared with those who underwent LG. Additionally, the frequencies of nodal involvement, more advanced stage of disease, total gastrectomy, D2 lymphadenectomy, and

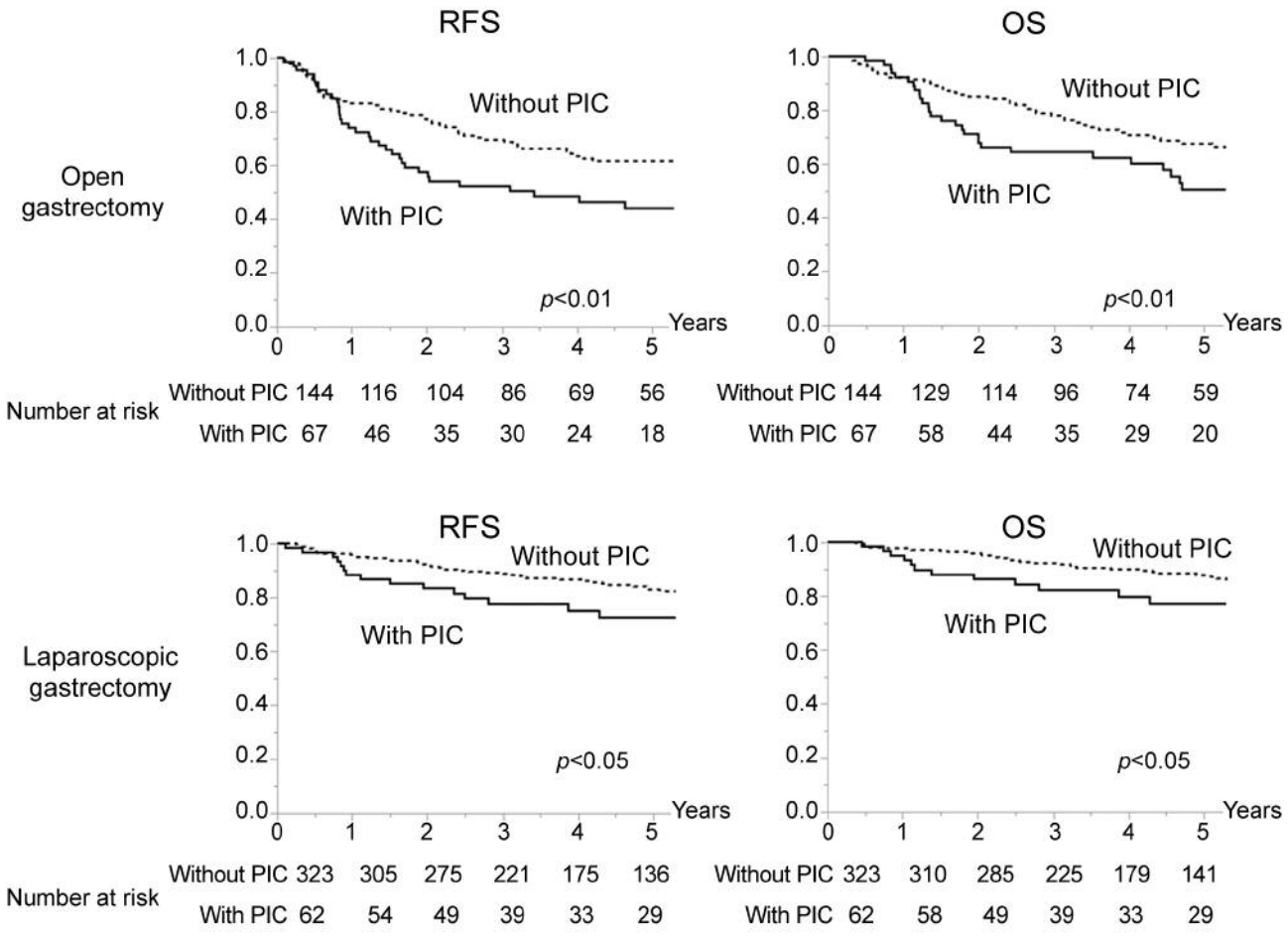

Figure 1. *RFS and OS after potentially curative gastrectomy in patients with or without PIC according to the surgical approach. RFS: Relapse-free survival; OS: overall survival; PIC: postoperative infectious complications.*

resection of other organs were higher in the OG group than the LG group. Shorter operating times, higher blood loss, blood transfusions, longer hospital stays, and PIC were more frequent in the OG group than the LG group.

The demographic and clinicopathological data of patients with or without PIC are presented in Table II. There were no differences in age, sex, body mass index, tumor location, tumor depth, nodal involvement, or stage between patients who underwent LG and OG. However, the rates of total gastrectomy, D2 lymphadenectomy, and combined resection of other organs were higher in patients who underwent OG compared to those who underwent LG among both the patients with and without PIC. In addition, the patients who underwent OG had shorter operating times and higher blood loss, and received blood transfusions more frequently. The patients who underwent OG had significantly longer postoperative hospital stays than those who underwent LG among the patients without PIC, but the postoperative hospital stay did not differ among the patients with PIC. The types and frequencies of PIC are depicted in Table III. The patients who underwent OG had pancreatic fistula and anastomotic leakage more frequently than those who underwent LG.

The main recurrence sites in LG and OG groups are shown in Table IV. There were no differences in the main recurrence sites between the OG and the LG groups and between patients with and without PIC.

The median follow-up of surviving patients was 1,574 days (range=113-3,502 days). There were significant differences in both the RFS and OS between the patients with and without PIC among those who underwent OG as well as those who underwent LG (Figure 1). Next, we compared the prognosis only in patients with Stage II and III gastric cancer because of extremely favorable and unfavorable outcomes in Stage I and IV gastric cancer, respectively (Figure 2). Although the patients with PIC among those who underwent OG tended to have worse RFS

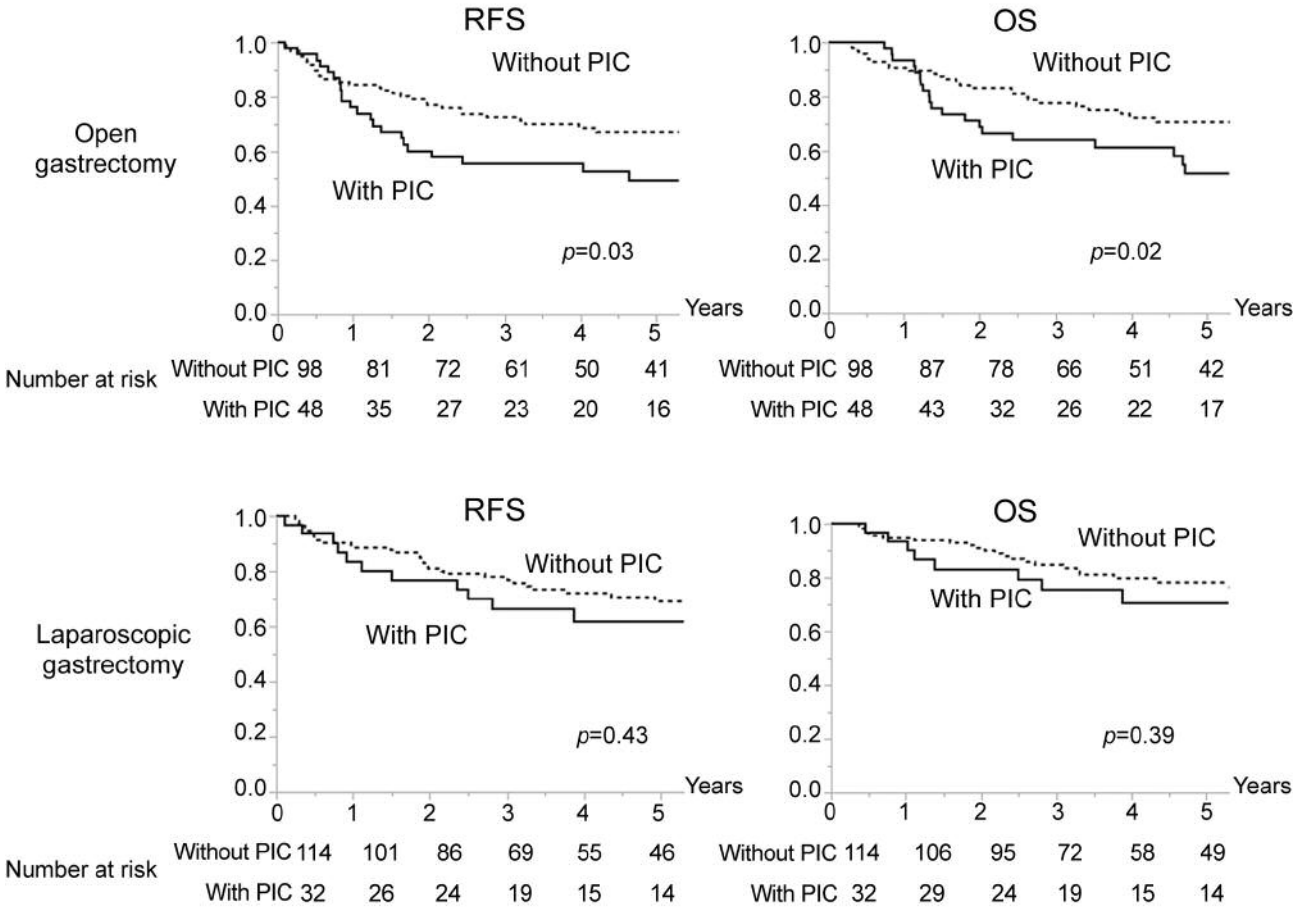

Figure 2. *RFS and OS after potentially curative gastrectomy in patients with or without PIC in patients with stage II or III gastric cancer. RFS: Relapse-free survival; OS: overall survival; PIC: postoperative infectious complications.*

and OS than those without PIC, the RFS and OS were not significantly different between the patients with and without PIC in the LG group.

In the univariate analysis, age, sex, BMI, tumor location, tumor size, blood transfusion, tumor depth, nodal involvement, and PIC significantly affected OS in all patients (Table V), and multivariate analysis demonstrated that age, BMI, and PIC were significantly associated with OS in this cohort. Although multivariate analysis demonstrated that nodal involvement and PIC were significantly associated with OS in patients undergoing OG, age and tumor depth, but not PIC, were associated with OS in patients undergoing LG.

Discussion

In this first report assessing the association of the type of gastrectomy for gastric cancer with PIC, PIC were negative predictors of clinical outcomes in patients with gastric cancer, particularly those who underwent OG, and the long-term prognosis may be impacted less by PIC in patients undergoing minimally invasive surgery, *i.e.* LG, as shown in multivariate and propensity score matching analyses.

Many reports have previously demonstrated a significant increase in long-term mortality in association with PIC (16-19). However, the precise mechanism underlying the relationship between long-term survival and PIC remains unclear. We previously suggested two possible mechanisms (8). First, enhancement of biological factors during infection or those produced by infection-causing bacteria may directly promote cancer cell proliferation and metastasis. For example, cytokines, oxygen free radicals, and lipopolysaccharides were implicated in promoting cancer cell growth (20-26). Second, dysregulated host immune response during infection may also contribute to tumorigenesis. Khuri *et al.* demonstrated an important independent predictive role for postoperative complications on both short- and long-term survival after major surgery (27). In that study, myocardial infarction and pneumonia,

but not wound infection, consistently exhibited a significant effect on long-term survival, suggesting that the long-term survival after surgery might depend on the degree of systemic immune response to the infection.

Systemic infection and sepsis were demonstrated to induce the systemic inflammatory response syndrome and lead to a period of immunosuppression, which is especially enhanced after surgical trauma (28-30). Relatedly, the "second attack" theory of multiple system organ failure (31) proposes that a severe insult in the form of infection or trauma primes the host immune system so that a subsequent, relatively trivial insult, produces a markedly exaggerated host immune response. This second attack hypothesis is being increasingly recognized as an important cause of morbidity and mortality following surgery and sepsis. Ogawa described that the term "second attack" is critically important for the prevention of organ dysfunction, because while surgeons cannot control the first insult, they can prevent or reduce the impact of the second attack (31). However, minimal invasive surgery, already utilized extensively, can reduce the impact of the first insult in the form of surgical trauma. Contrary to the concept of the second attack, prior exposure of innate immune cells, such as macrophages, to minute amounts of endotoxins promote their refractoriness to subsequent endotoxin challenges, a phenomenon termed "endotoxin tolerance" (32). These conflicting responses may arise from differences in the degree and/or content of the initial insult. In that regard, it is reasonable to expect that the difference in the degree of surgical invasiveness during gastrectomy will affect the biological response after PIC and the unfavorable outcomes associated with PIC.

Although many prospective studies aimed to determine whether minimally invasive surgical approaches such as endoscopic or robotic surgery contribute to the oncological prognosis compared to conventional open surgery, the results remain controversial (33, 34). One potential explanation is that the incidence of PIC and their effect on long-term prognosis are not always considered.

In conclusion, our findings indicate that PIC are useful predictors of adverse clinical outcomes in patients with gastric cancer, particularly those undergoing open surgery, and that the long-term prognosis of patients undergoing minimally invasive surgery might be impacted less by PIC. The current study did not demonstrate any differences in postoperative biological parameters such as serum cytokine levels between the two groups, which is a limitation of the study; further studies evaluating immunological parameters and cytokine levels will be essential to elucidate the mechanism underlying the current findings. Future prospective trials are required to investigate whether differential surgical approaches are associated with differences in long-term prognosis in association with postoperative complications due to infections.

Table V. *Univariate and multivariate analyses of factors that may affect overall survival.*

Variables	All patients						Open gastrectomy						Laparoscopic gastrectomy					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age (>70 years old)	2.9	2.0-4.3	<0.01	2.8	1.9-4.1	<0.01	1.6	1.0-2.5	0.06	-	-	-	6.8	3.5-14.8	<0.01	6.3	3.2-14.1	<0.01
Gender (male)	1.6	1.0-2.5	0.03	1.6	1.0-2.5	0.40	1.8	1.0-3.4	0.06	-	-	-	1.3	0.7-2.7	0.35	-	-	-
BMI (<22)	1.6	1.1-2.2	<0.01	1.8	1.3-2.6	<0.01	1.4	0.9-2.2	0.17	-	-	-	1.6	1.0-2.8	0.06	-	-	-
Tumor location (U)	1.5	1.0-2.1	0.03	1.2	0.8-1.7	0.38	1.2	0.7-1.8	0.53	-	-	-	1.5	0.8-2.7	0.17	-	-	-
Tumor size (>50 mm)	1.8	1.3-2.5	<0.01	1.0	0.7-1.5	>0.99	1.3	0.8-2.1	0.27	-	-	-	1.1	0.6-2.1	0.68	-	-	-
Blood transfusion (yes)	2.4	1.5-3.8	<0.01	1.0	0.6-1.6	0.91	1.5	0.9-2.5	0.15	-	-	-	1.9	0.3-6.2	0.41	-	-	-
Histology (intestinal type)	1.2	0.8-1.7	0.30	-	-	-	1.0	0.6-1.6	0.90	-	-	-	1.8	1.0-3.3	<0.05	1.8	1.0-3.4	0.04
Tumor depth (compared with T1) T2, T3, T4	3.3	2.3-4.9	<0.01	2.3	1.5-3.7	<0.01	2.0	1.0-4.3	0.03	1.4	0.7-3.2	0.33	3.0	1.8-5.1	<0.01	3.5	1.9-6.5	<0.01
Nodal involvement (compared with N0) N1, N2, N3	3.1	2.2-4.4	<0.01	1.8	1.2-2.8	<0.01	2.6	1.5-4.8	<0.01	2.4	1.4-4.6	<0.01	2.2	1.3-3.9	<0.01	1.0	0.5-1.9	0.95
Postoperative infectious complications (yes)	2.2	1.5-3.1	<0.01	2.0	1.3-2.9	<0.01	1.8	1.2-2.9	<0.05	1.9	1.2-3.0	<0.01	1.7	0.9-3.1	0.11	-	-	-

PIC: Postoperative infectious complications; OG: open gastrectomy; LG: laparoscopic gastrectomy; CI: confidence interval.

Conflicts of Interest

All Authors (Hiromi Nagata, Hironori Tsujimoto, Yoshihisa Yaguchi, Keita Kouzu, Yujiro Itazaki, Yusuke Ishibashi, Satoshi Tsuchiya, Takao Sugihara, Nozomi Ito, Manabu Harada, Shinsuke Nomura, Yoji Kishi, Hideki Ueno) report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Authors' Contributions

Dr. Hiromi Nagata and Dr. Hironori Tsujimoto conceived the idea of this research, designed the protocol, and supervised the analysis of the results. Yoshihisa Yaguchi, Keita Kouzu, Yujiro Itazaki, Yusuke Ishibashi, Satoshi Tsuchiya, Takao Sugihara, Nozomi Ito, Manabu Harada, Shinsuke Nomura developed and supervised all works and analyzed the results. Dr. Yoji Kishi and Hideki Ueno supervised the study.

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