Am J Cancer Res 2023;13(12):6063-6071
www.ajcr.us /ISSN:2156-6976/ajcr0152096

Original Article

Pancreatic fistula as a pivotal prognostic factor among postoperative complications in gastric cancer

Ryo Ishida*, Shuhei Komatsu*, Yusuke Takashima, Keiji Nishibeppu, Takuma Ohashi, Toshiyuki Kosuga, Hirotaka Konishi, Atsushi Shiozaki, Takeshi Kubota, Hitoshi Fujiwara, Eigo Otsuji

Division of Digestive Surgery, Department of Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan.
**Equal contributors.*

Received July 8, 2023; Accepted November 29, 2023; Epub December 15, 2023; Published December 30, 2023

Abstract: Recent studies have identified that postoperative infectious complications (PICs) have contributed to poor prognosis in gastric cancer (GC). In this study, we investigated which complication among PICs most strongly contributes to a poor prognosis. This study included 1,653 consecutive patients who underwent curative gastrectomy for GC between 1997 and 2018. A Clavien-Dindo classification of grade II or higher was used as a cut-off for PICs. PICs occurred in 17.1% of all GC patients. Patients with a PIC had a poorer prognosis than those without [Hazard ratio (HR): 17.5, $P < 0.001$]. Among PICs, pancreatic fistula (PF) had the strongest effect on poor prognosis (HR: 3.16) compared to anastomotic leakage (HR: 2.41), pneumonia (HR: 2.11) and intra-abdominal abscess (HR: 1.98). Multivariate analysis on pStage II or III GC showed that PF had the strongest poor prognostic effect ($P = 0.025$, HR: 2.21, 95%-CI: 1.07-3.99). Patients with PF had significantly higher C-reactive protein (CRP) levels on postoperative days 1 ($P = 0.039$) and 3 ($P = 0.044$), tended to experience a prolonged period of high inflammation, with CRP levels above 10 mg/dL ($P = 0.086$), and had the highest incidence of recurrence compared to other PICs. Robotic gastrectomy had no incidence of PF, while open gastrectomy resulted in a 2% occurrence, and laparoscopic gastrectomy had a 1.8% occurrence. In conclusion, PF had the strongest effect on poor prognosis among PICs. Robotic gastrectomy might be the optimal approach for avoiding PF.

Keywords: Pancreatic fistula, postoperative complication, prognosis, gastric cancer

Introduction

Although various treatments for gastric cancer (GC) have improved considerably in recent decades [1-3], curative gastrectomy remains the most pivotal strategy for GC patients [4-6]. Curative gastrectomy with radical lymphadenectomy is the most effective treatment for improving prognosis of the patients with resectable GC; however, postoperative infectious complications (PICs) have a negative prognostic effect [7-9]. Among PICs, pneumonia [10], anastomotic leakage (AL) [11], intraabdominal abscesses [7, 12] and pancreatic fistula (PF) [13, 14] have been commonly reported to contribute to worse prognosis. In addition, previous studies have already identified that the severe inflammation of PICs affects negative immunological responses leading to the development and progression of micro-metastatic and residual cancer cells [15, 16]. However, it remains unclear which complication among PICs most strongly contributes to a poor prognosis. Therefore, verifying the prognostic effect of each type of PIC and identifying which types should specifically be targeted in an effort to improve prognosis are pivotal issues.

In this study, we clarified which PICs have the greatest prognostic impact and discussed better surgical approach to reduce the incidence of PICs. Our results may provide evidence that pancreatic fistula is a pivotal prognostic issue among PICs, which should specifically be targeted in an effort to improve prognosis.

Materials and methods

Patients and surgical procedures

This study was approved by the Kyoto Prefectural University of Medicine, Japan, and was therefore performed in accordance with the ethical standards laid down in the Declaration of

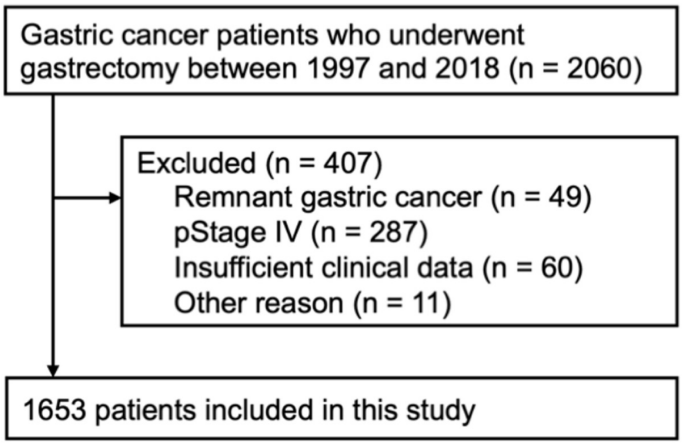

Figure 1. Patients enrolled in this study. A total of 2,060 patients underwent curative gastrectomy with lymphadenectomy between January 1997 and December 2018. Of these, 407 patients were excluded from the study. Thus, data from 1,653 consecutive patients were obtained from their hospital records and retrospectively analyzed.

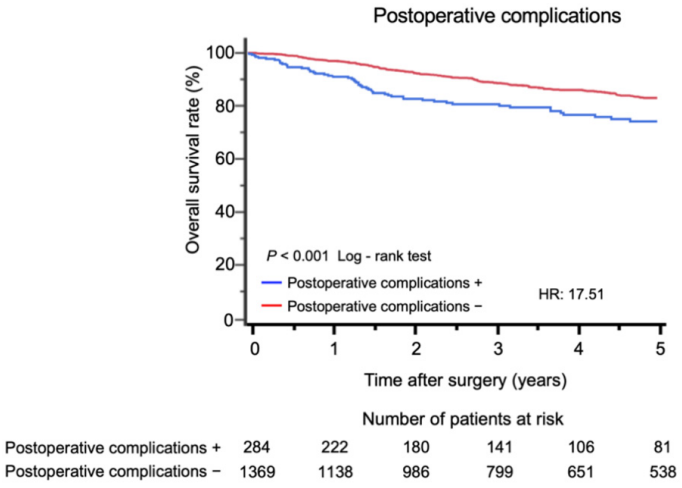

Figure 2. Overall survival curves of patients with and without postoperative complications. Patients with PICs had a significantly poorer overall survival compared to those without.

Helsinki. Written informed consent to participate in the research was obtained from all patients. A total of 1,653 consecutive patients who underwent curative gastrectomy with lymphadenectomy for GC at our institute between January 1997 and June 2018 were included in this study. Patients with Stage IV cancer and patients with remnant GC were excluded (**Figure 1**).

Based on preoperative diagnosis using gastric endoscopy and computed tomography scans, total or distal gastrectomy with sufficient lymphadenectomy was performed, mainly according to the Japanese guidelines for the treatment of GC [17]. Patients with clinical T1 and N0 tumors underwent D1 or D1+ lymphadenectomy, and patients with clinical T2 or more advanced tumors or those with N1 or more advanced tumors (or both) underwent D2 or D2+ lymphadenectomy. In D2 dissections, the perigastric lymph nodes and all second-tier lymph nodes were completely retrieved.

Follow-up after curative gastrectomy

Postoperative follow-up was performed in the outpatient clinic every three months following surgery. Blood chemistry was also measured every three months. Endoscopic examinations were performed annually, and computed tomography examinations were performed every three months for five years after surgery.

Definition of postoperative complications

A Clavien-Dindo classification of grade II or higher was the cut-off for PIC. Postoperative PF was retrospectively defined as an output via an operatively placed drain of any measurable fluid volume on or after postoperative day 3 with an amylase content more than three times higher than the upper normal serum value. An intraabdominal abscess was defined as an intraabdominal infection excluding PF and anastomotic leakage.

Statistical analysis

Statistical analysis was performed using JMP version 16 (ASA Institute, Cary, NC, USA). The Chi-squared test and Fisher's exact probability test were performed for comparing categorical variables, and the Student's *t*-test and Mann-Whitney *U* test for unpaired continuous variables were performed to compare clinicopathological characteristics between two groups. Survival curves were estimated using the Kaplan-Meier method, and statistical differences were examined using the log-rank test. Univariate and multivariate survival analyses

Table 1. Prognostic effect of each type of postoperative infectious complication

		HR[a]	95% CI[b]
Pancreatic fistula	Positive vs. Negative	3.16	1.68-5.95
Anastomotic Leakage	Positive vs. Negative	2.41	1.44-3.95
Pneumonia	Positive vs. Negative	2.11	1.05-4.28
Intraabdominal abscess	Positive vs. Negative	1.98	1.05-3.73

[a]HR: hazard ratio; [b]CI: confidence interval.

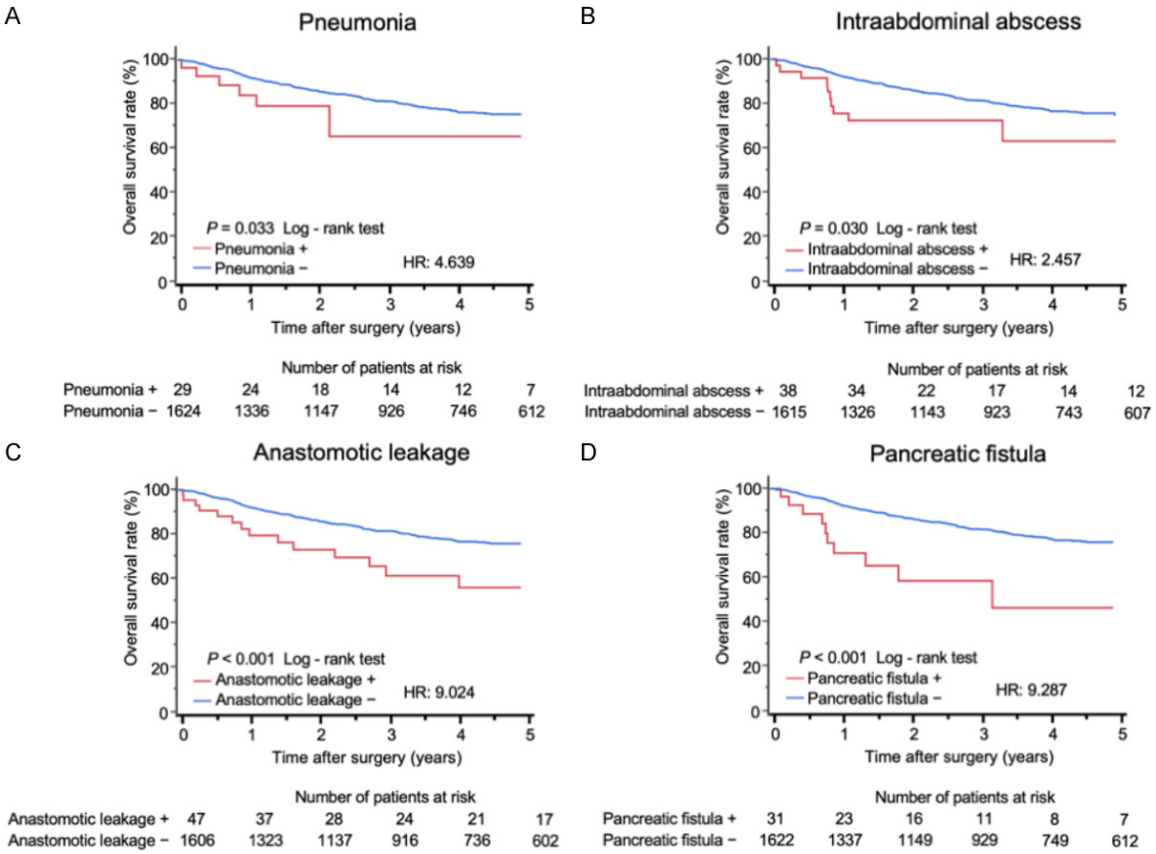

Figure 3. Overall survival curves of patients with and without each type of postoperative complication. PF had the strongest impact on prognosis compared with the other types; AL, intraabdominal abscesses, and pneumonia.

were performed using the likelihood ratio test of the stratified Cox proportional hazards model. $P < 0.05$ was considered statistically significant.

Results

Prognostic effects of PICs for GC patients

PICs occurred in 17.1% (284/1653) of all GC patients. Of these, 31 patients (1.9%) had PF, 46 patients (2.7%) had AL, 38 (2.3%) patients had intraabdominal abscesses, and 29 patients (1.8%) had pneumonia. Patients with PICs had a significantly poorer overall survival (OS) compared to those without ($P < 0.001$, with a complication vs. without a complication: 74.3% vs. 83.1%; **Figure 2**). When analyzed for each type of PIC, PF had the strongest impact on prognosis ($P < 0.001$, HR: 3.16, 95% confidence interval [CI]: 1.68-5.95) compared with the other types; AL ($P < 0.001$, HR: 2.38, 95%-CI: 1.44-3.95), intraabdominal abscesses ($P = 0.030$, HR: 1.98, 95%-CI: 1.05-3.73), and pneumonia ($P = 0.033$, HR: 2.11, 95%-CI: 1.05-4.28; **Table 1** and **Figure 3**). Multivariate analyses using Cox's proportional hazards model revealed that PF was an independent poor prognostic factor for pStage II-III GC patients ($P = 0.029$, HR: 2.08, 95%-CI: 1.07-3.99; **Table 2**).

Table 2. Results of univariate and multivariate analyses

Variables	Univariate[a]	Multivariate[b]		
	P-value	HR[c]	95% CI[d]	*P*-value
Sex				
Male vs. Female	0.484	1.21	0.88-1.67	0.238
Age (years)				
75 ≤ vs. < 75	**< 0.001**	2.13	1.53-2.96	**< 0.001**
Tumor size (mm)				
50 ≤ vs. < 50	**< 0.001**	1.40	1.00-1.94	**0.050**
pT category[e]				
pT3-4 vs. pT1-2	**< 0.001**	2.80	1.62-4.87	**< 0.001**
pN category[e]				
pN1-3 vs. pN0	**< 0.001**	1.86	1.23-2.81	**0.003**
Lymphatic invasion				
Positive vs. Negative	**< 0.001**	1.69	1.10-2.60	**0.016**
Venous invasion				
Positive vs. Negative	**< 0.001**	1.12	0.81-1.54	0.492
Pancreatic fistula				
Positive vs. Negative	**< 0.001**	2.08	1.07-3.99	**0.029**
Anastomotic Leakage				
Positive vs. Negative	**< 0.001**	1.26	0.60-2.62	0.531
Pneumonia				
Positive vs. Negative	**0.033**	0.71	0.51-3.87	0.495
Intraabdominal abscess				
Positive vs. Negative	**0.030**	0.95	0.45-2.40	0.911

[a]Analyzed by log-rank test; [b]analyzed by Cox's proportional hazard model; [c]HR: hazard ratio; [d]CI: confidence interval; [e]Classified according to the Japanese Classification of Gastric Carcinoma. Significant *P*-values are shown in bold.

Clinicopathological factors and PF

Next, we evaluated potential associations between PF and clinicopathological factors. As shown in **Table 3**, PF in GC patients was significantly associated with an advanced T stage ($P = 0.004$), advanced N stage ($P = 0.008$), lymphatic invasion ($P = 0.023$), and vessel invasion ($P = 0.016$), and tended to be more common in males ($P = 0.100$). Regarding surgical approaches, the incidence of PF was lower in robotic gastrectomy (0%) than in other approaches: 2.0% (21/1048) in open gastrectomy and 1.8% (10/571) in laparoscopic gastrectomy.

Serum C-reactive protein levels and recurrence patterns of each type of PIC

To investigate differences in postoperative inflammation in each type of PIC, we compared trends in serum C-reactive protein (CRP) levels. As a result, CRP levels were significantly higher in patients with PF than in patients with other PICs on postoperative day (POD) 1 ($P = 0.039$; Pneumonia vs. Intraabdominal abscess vs. AL vs. PF: median serum CRP level, 6.5 vs. 7.3 vs. 7.4 vs. 8.5 mg/dL) and POD 3 ($P = 0.044$; Pneumonia vs. Intraabdominal abscess vs. AL vs. PF: median serum CRP level, 12.1 vs. 14.9 vs. 12.2 vs. 18.0 mg/dL; **Figure 4**). Furthermore, the number of postoperative days with CRP levels exceeding 10 mg/dL tended to be higher with PF than among the other PICs ($P = 0.086$; Pneumonia vs. Intraabdominal abscess vs. AL vs. PF: median number of days above CRP 10 mg/dL, 3.5 vs. 7.0 vs. 8.0 vs. 8.0; **Figure 4**). Regarding the recurrence patterns, patients with PF had more peritoneal recurrences (n = 8, 20.0%) than patients with other PICs (**Figure 5**).

Discussion

GC is one of the most common causes of cancer-related death worldwide [18]. Despite recent advances in surgical approaches, postoperative complications still occur in GC [19-21] and have a negative prognostic effect [8, 19, 22-25]. However, there have been no reports about differences in prognosis from various types of postoperative complications, especially in PICs of GC. In this study, we demonstrated that PF (HR: 3.16) had the strongest effect on poor prognosis among various types of PIC in GC, followed by AL (HR: 2.41), pneumonia (HR: 2.11), and intra-abdominal abscess (HR: 1.98). Our results provide evidence that PF is a pivotal issue that should specifically be targeted in an effort to improve prognosis.

There are two putative reasons regarding the poor prognostic effect of PF associated with GC. The first reason is a cancer-activation effect due to the infection-induced inflammatory response. Previous studies demonstrated that the infection-induced inflammatory response facilitated the aggressive features of tumor cells through inflammatory cells and cytokines such as TNF-α, IL6, PDGF, and VEGF [26, 27]. Indeed, in our study, postoperative

Table 3. Associations between postoperative fistula and clinicopathological factors

Variables	Pancreatic fistula		*P*-value*
	Positive (n = 31)	Negative (n = 1622)	
Sex			
Male	25 (81%)	1088 (67%)	0.100
Female	6 (19%)	534 (33%)	
Age (years)			
≥ 75	8 (26%)	357 (22%)	0.620
< 75	23 (74%)	1265 (78%)	
pT category			
T3-4	16 (52%)	454 (28%)	**0.004**
T1-2	15 (48%)	1168 (72%)	
pN category			
N1-3	17 (55%)	444 (27%)	**0.008**
N0	14 (45%)	1177 (73%)	
Lymphatic invasion			
Positive	19 (61%)	662 (41%)	**0.023**
Negative	12 (39%)	960 (59%)	
Venous invasion			
Positive	16 (52%)	497 (31%)	**0.016**
Negative	15 (48%)	1125 (69%)	
Operative procedure			
Open	21 (68%)	1048 (65%)	0.746
Laparoscopic	10 (32%)	561 (34%)	
Robotic	0 (0%)	13 (1%)	
Tumor major axis (mm)			
≥ 50	12 (39%)	442 (27%)	0.171
< 50	19 (61%)	1180 (73%)	

*P-values are from the Chi-squared test or Fisher's exact test. Significant *P*-values are shown in bold.

CRP levels were considerably higher, and there were more postoperative days with elevated CRP levels in patients with PF compared with other PICs. Moreover, patients with PF proved to have significantly more recurrences, particularly peritoneal recurrence. To our knowledge, these findings have not been reported previously. The second reason is the delayed administration of adjuvant chemotherapy because PF was strongly associated with a longer hospital stay. Previous studies, including our own, clearly demonstrate that the delayed initiation of adjuvant chemotherapy affects poor prognosis for GC patients [28, 29]. Thus, PF might have the strongest poor prognostic impact in GC.

Risk factors of PF have already been reported, such as advanced age and obesity [14]. Also, we have also reported on the risk factors of severe PF [30]. In recent years, surgical procedures have been reported as a possible risk factor. Laparoscopic gastrectomy for GC is widespread as a minimally invasive surgical technique, and the clinical significance of early and long-term outcomes has been established [31, 32], even for advanced cancers [33-35]. Moreover, laparoscopic gastrectomy contributes to reducing postoperative pulmonary and cardiac events [36]. However, the incidence of PF is equivalent to or more common after laparoscopic surgery compared with open surgery because of its technical difficulty in lymphadenectomy around the pancreas [37]. Whereas in robotic surgery, recent prospective and RCT studies identified reduced postoperative complications and PICs, particularly in PF, compared with laparoscopic surgery [20, 38]. Indeed, fascinating preliminary result in our study is that there were no patients with PF following robotic gastrectomy (0%). In contrast, PF occurred in 1.8% (10/571) after laparoscopic gastrectomy and 2.0% (21/1048) of patients

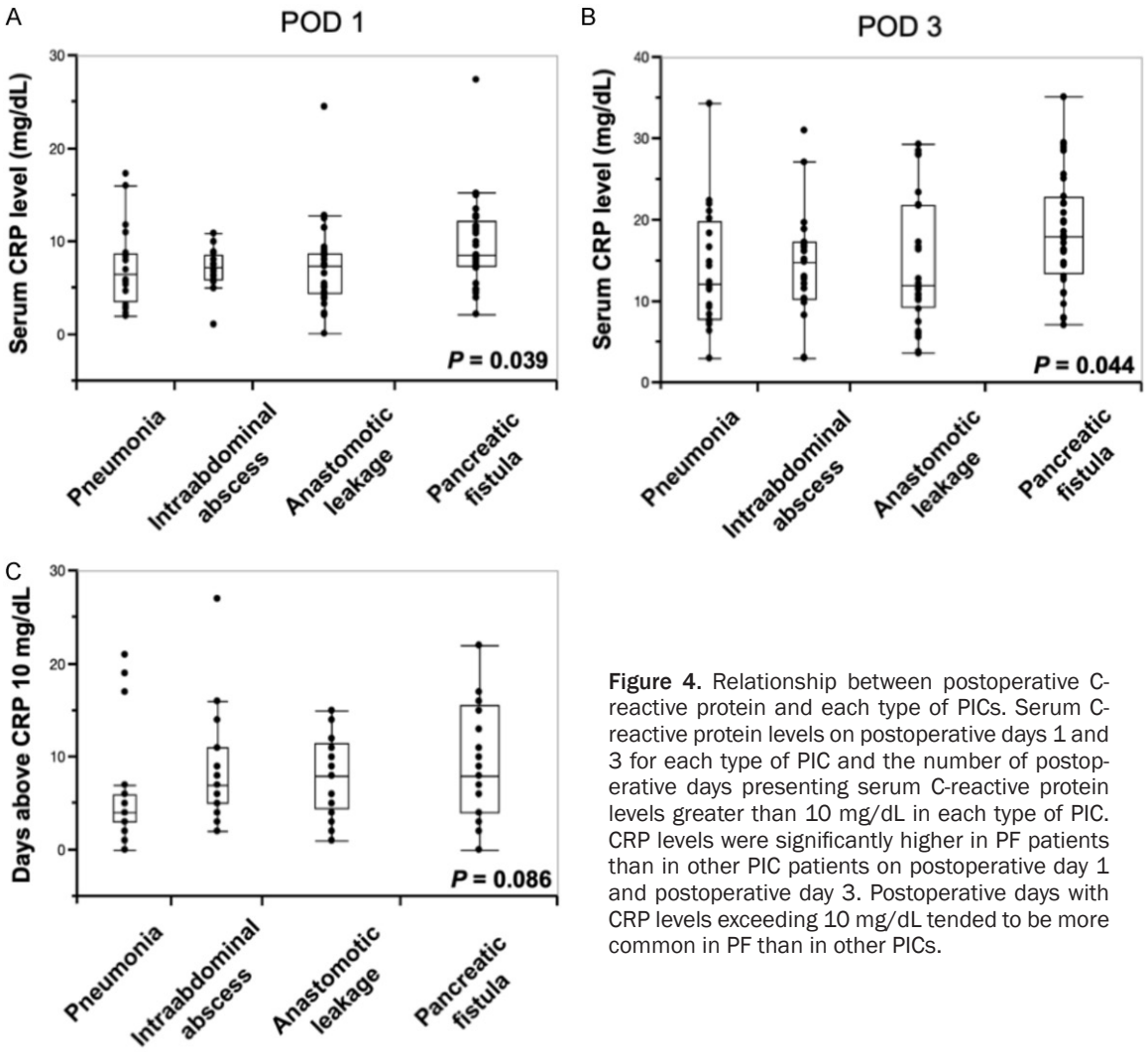

Figure 4. Relationship between postoperative C-reactive protein and each type of PICs. Serum C-reactive protein levels on postoperative days 1 and 3 for each type of PIC and the number of postoperative days presenting serum C-reactive protein levels greater than 10 mg/dL in each type of PIC. CRP levels were significantly higher in PF patients than in other PIC patients on postoperative day 1 and postoperative day 3. Postoperative days with CRP levels exceeding 10 mg/dL tended to be more common in PF than in other PICs.

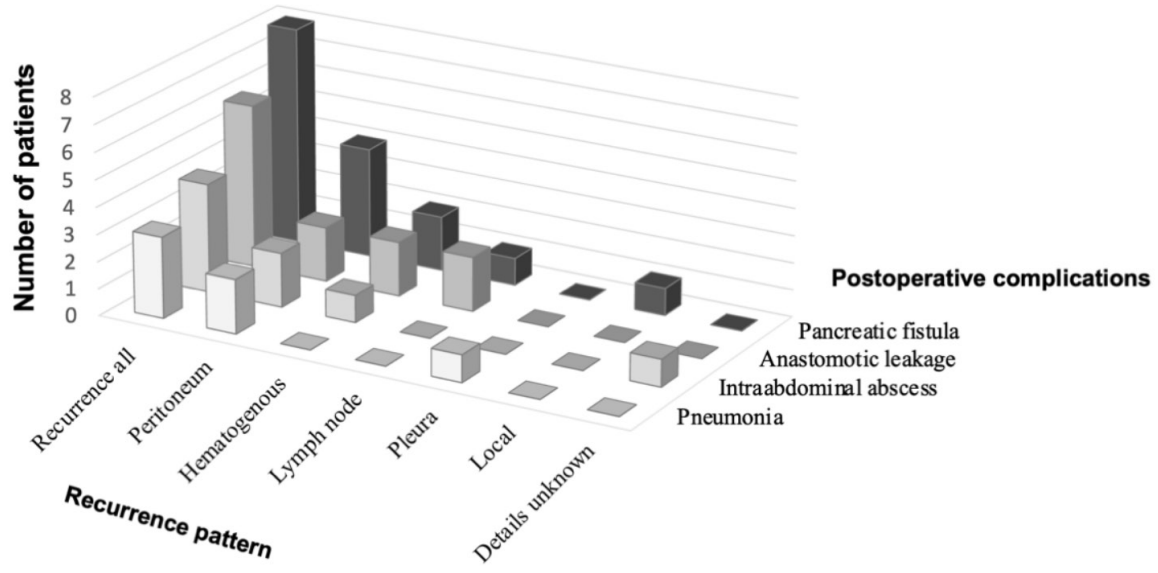

Figure 5. The incidence of recurrences associated with the PICs. Patients with PF proved to have significantly more recurrences, particularly peritoneal recurrences.

following open gastrectomy. Regarding the short-term outcomes comparing recent robotic surgery cases between June 2018 and November 2023, the incidence of PF was significantly lower in the robotic surgery group (0/110) compared to the non-robotic surgery group (34/1853) (Robotic surgery vs. non-robotic surgery: 0% vs. 1.8%, $P = 0.047$; data not shown).

A recent study identified decreased postoperative complications and improved long-term survival following robotic surgery for GC [39]. Robotic surgery has various technical merits, such as 3-D vision, easier instrument movement, and tremor filtration, which enable surgeons to address the surgical field safely and easily. Thus, robotic gastrectomy is feasible and safe to avoid postoperative PF [40, 41]. Robotic surgery might be expected to improve long-term outcomes in GC patients by reducing inflammation and avoiding PF.

Our study had a limitation. Primarily, the results were retrospectively demonstrated with a small cohort. The long accrual period of this retrospective analysis at a single institute may have included possible treatment variations. Therefore, a prospective observational study using several large cohorts or a nationwide clinical database study may be needed to validate our finding that PF is a pivotal prognostic issue among PICs. Nevertheless, PF should specifically be targeted in an effort to improve prognosis using robotic surgery.

Disclosure of conflict of interest

None.

Abbreviations

GC, gastric cancer; PIC, postoperative infectious complications; PF, Pancreatic fistula; AL, Anastomotic leakage; CRP, C-reactive protein; POD, postoperative day; OS, overall survival; HR, Hazard ratio; CI, Confidence interval.

Address correspondence to: Dr. Shuhei Komatsu, Division of Digestive Surgery, Department of Surgery, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachihirokoji, Kamigyo-ku, Kyoto 602-8566, Japan. Tel: +81-75-2515527; Fax: +81-75-2515522; E-mail: skomatsu@koto.kpu-m.ac.jp

References

[1] Chen ZD, Zhang PF, Xi HQ, Wei B, Chen L and Tang Y. Recent advances in the diagnosis, staging, treatment, and prognosis of advanced gastric cancer: a literature review. Front Med (Lausanne) 2021; 8: 744839.

[2] Kono K, Nakajima S and Mimura K. Current status of immune checkpoint inhibitors for gastric cancer. Gastric Cancer 2020; 23: 565-578.

[3] Harada K, Mizrak Kaya D, Shimodaira Y and Ajani JA. Global chemotherapy development for gastric cancer. Gastric Cancer 2017; 20 Suppl 1: 92-101.

[4] Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A and Arnold D; ESMO Guidelines Committee. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016; 27 Suppl 5: v38-v49.

[5] Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer 2021; 24: 1-21.

[6] Komatsu S and Otsuji E. Essential updates 2017/2018: recent topics in the treatment and research of gastric cancer in Japan. Ann Gastroenterol Surg 2019; 3: 581-591.

[7] Tokunaga M, Tanizawa Y, Bando E, Kawamura T and Terashima M. Poor survival rate in patients with postoperative intra-abdominal infectious complications following curative gastrectomy for gastric cancer. Ann Surg Oncol 2013; 20: 1575-1583.

[8] Ebihara Y, Kyogoku N, Murakami Y, Murakawa K, Nakamura F, Morita T, Okushiba S and Hirano S. Relationship between laparoscopic total gastrectomy-associated postoperative complications and gastric cancer prognosis. Updates Surg 2023; 75: 149-158.

[9] Shimada H, Fukagawa T, Haga Y and Oba K. Does postoperative morbidity worsen the oncological outcome after radical surgery for gastrointestinal cancers? A systematic review of the literature. Ann Gastroenterol Surg 2017; 1: 11-23.

[10] Kiuchi J, Komatsu S, Ichikawa D, Kosuga T, Okamoto K, Konishi H, Shiozaki A, Fujiwara H, Yasuda T and Otsuji E. Putative risk factors for postoperative pneumonia which affects poor prognosis in patients with gastric cancer. Int J Clin Oncol 2016; 21: 920-926.

[11] Walker KG, Bell SW, Rickard MJ, Mehanna D, Dent OF, Chapuis PH and Bokey EL. Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. Ann Surg 2004; 240: 255-259.

[12] Fujiya K, Tokunaga M, Mori K, Makuuchi R, Tanizawa Y, Bando E, Kawamura T and Terashima M. Long-term survival in patients with postoperative intra-abdominal infectious complications after curative gastrectomy for gastric cancer: a propensity score matching analysis. Ann Surg Oncol 2016; 23 Suppl 5: 809-816.
[13] Kanda M, Ito S, Mochizuki Y, Teramoto H, Ishigure K, Murai T, Asada T, Ishiyama A, Matsushita H, Tanaka C, Kobayashi D, Fujiwara M, Murotani K and Kodera Y. Multi-institutional analysis of the prognostic significance of postoperative complications after curative resection for gastric cancer. Cancer Med 2019; 8: 5194-5201.
[14] Katai H, Yoshimura K, Fukagawa T, Sano T and Sasako M. Risk factors for pancreas-related abscess after total gastrectomy. Gastric Cancer 2005; 8: 137-141.
[15] Mynster T, Christensen IJ, Moesgaard F and Nielsen HJ. Effects of the combination of blood transfusion and postoperative infectious complications on prognosis after surgery for colorectal cancer. Danish RANX05 Colorectal Cancer Study Group. Br J Surg 2000; 87: 1553-1562.
[16] Sierzega M, Kolodziejczyk P and Kulig J; Polish Gastric Cancer Study Group. Impact of anastomotic leakage on long-term survival after total gastrectomy for carcinoma of the stomach. Br J Surg 2010; 97: 1035-1042.
[17] Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011; 14: 101-112.
[18] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.
[19] Yasunaga H, Horiguchi H, Kuwabara K, Matsuda S, Fushimi K, Hashimoto H and Ayanian JZ. Outcomes after laparoscopic or open distal gastrectomy for early-stage gastric cancer: a propensity-matched analysis. Ann Surg 2013; 257: 640-646.
[20] Uyama I, Suda K, Nakauchi M, Kinoshita T, Noshiro H, Takiguchi S, Ehara K, Obama K, Kuwabara S, Okabe H and Terashima M. Clinical advantages of robotic gastrectomy for clinical stage I/II gastric cancer: a multi-institutional prospective single-arm study. Gastric Cancer 2019; 22: 377-385.
[21] Kim HH, Han SU, Kim MC, Hyung WJ, Kim W, Lee HJ, Ryu SW, Cho GS, Song KY and Ryu SY. Long-term results of laparoscopic gastrectomy for gastric cancer: a large-scale case-control and case-matched Korean multicenter study. J Clin Oncol 2014; 32: 627-633.
[22] Kubota T, Hiki N, Sano T, Nomura S, Nunobe S, Kumagai K, Aikou S, Watanabe R, Kosuga T and Yamaguchi T. Prognostic significance of complications after curative surgery for gastric cancer. Ann Surg Oncol 2014; 21: 891-898.
[23] Powell A, Coxon AH, Patel N, Chan D, Christian A and Lewis W. Prognostic significance of postoperative morbidity severity score after potentially curative D2 gastrectomy for carcinoma. J Gastrointest Surg 2018; 22: 1516-1527.
[24] Takeuchi D, Koide N, Suzuki A, Ishizone S, Shimizu F, Tsuchiya T, Kumeda S and Miyagawa S. Postoperative complications in elderly patients with gastric cancer. J Surg Res 2015; 198: 317-326.
[25] Nagata T, Adachi Y, Taniguchi A, Kimura Y, Iitaka D, Iwata G and Yamaoka N. Prognostic impacts of categorized postoperative complications in surgery for gastric cancer. Asian J Surg 2023; 46: 451-457.
[26] Coussens LM and Werb Z. Inflammation and cancer. Nature 2002; 420: 860-867.
[27] Dvorak HF. Tumors: wounds that do not heal-redux. Cancer Immunol Res 2015; 3: 1-11.
[28] Fujitani K, Kurokawa Y, Takeno A, Endoh S, Ohmori T, Fujita J, Yamasaki M, Takiguchi S, Mori M and Doki Y; Osaka University Clinical Research Group for Gastroenterological Surgery. Time to initiation or duration of S-1 adjuvant chemotherapy; which really impacts on survival in stage II and III gastric cancer? Gastric Cancer 2018; 21: 446-452.
[29] Takashima Y, Komatsu S, Nishibeppu K, Kiuchi J, Ohashi T, Shimizu H, Arita T, Yamamoto Y, Konishi H, Morimura R, Shiozaki A, Kuriu Y, Ikoma H, Kubota T, Fujiwara H, Okamoto K and Otsuji E. Clinical impact of postoperative interval until adjuvant chemotherapy following curative gastrectomy for advanced gastric cancer. J Cancer 2021; 12: 5960-5966.
[30] Komatsu S, Ichikawa D, Kashimoto K, Kubota T, Okamoto K, Konishi H, Shiozaki A, Fujiwara H and Otsuji E. Risk factors to predict severe postoperative pancreatic fistula following gastrectomy for gastric cancer. World J Gastroenterol 2013; 19: 8696-8702.
[31] Katai H, Mizusawa J, Katayama H, Morita S, Yamada T, Bando E, Ito S, Takagi M, Takagane A, Teshima S, Koeda K, Nunobe S, Yoshikawa T, Terashima M and Sasako M. Survival outcomes after laparoscopy-assisted distal gastrectomy versus open distal gastrectomy with nodal dissection for clinical stage IA or IB gastric cancer (JCOG0912): a multicentre, non-inferiority, phase 3 randomised controlled trial. Lancet Gastroenterol Hepatol 2020; 5: 142-151.

[32] Kim W, Kim HH, Han SU, Kim MC, Hyung WJ, Ryu SW, Cho GS, Kim CY, Yang HK, Park DJ, Song KY, Lee SI, Ryu SY, Lee JH and Lee HJ; Korean Laparo-endoscopic Gastrointestinal Surgery Study (KLASS) Group. Decreased morbidity of laparoscopic distal gastrectomy compared with open distal gastrectomy for stage I gastric cancer: short-term outcomes from a multicenter randomized controlled trial (KLASS-01). Ann Surg 2016; 263: 28-35.

[33] Etoh T, Ohyama T, Sakuramoto S, Tsuji T, Lee SW, Yoshida K, Koeda K, Hiki N, Kunisaki C, Tokunaga M, Otsubo D, Takagane A, Misawa K, Kinoshita T, Cho H, Doki Y, Nunobe S, Shiraishi N and Kitano S; Japanese Laparoscopic Surgery Study Group (JLSSG). Five-year survival outcomes of laparoscopy-assisted vs open distal gastrectomy for advanced gastric cancer: the JLSSG0901 randomized clinical trial. JAMA Surg 2023; 158: 445-454.

[34] Yu J, Huang C, Sun Y, Su X, Cao H, Hu J, Wang K, Suo J, Tao K, He X, Wei H, Ying M, Hu W, Du X, Hu Y, Liu H, Zheng C, Li P, Xie J, Liu F, Li Z, Zhao G, Yang K, Liu C, Li H, Chen P, Ji J and Li G; Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group. Effect of laparoscopic vs open distal gastrectomy on 3-year disease-free survival in patients with locally advanced gastric cancer: the CLASS-01 randomized clinical trial. JAMA 2019; 321: 1983-1992.

[35] Hu Y, Huang C, Sun Y, Su X, Cao H, Hu J, Xue Y, Suo J, Tao K, He X, Wei H, Ying M, Hu W, Du X, Chen P, Liu H, Zheng C, Liu F, Yu J, Li Z, Zhao G, Chen X, Wang K, Li P, Xing J and Li G. Morbidity and mortality of laparoscopic versus open D2 distal gastrectomy for advanced gastric cancer: a randomized controlled trial. J Clin Oncol 2016; 34: 1350-1357.

[36] Inokuchi M, Kumamaru H, Nakagawa M, Miyata H, Kakeji Y, Seto Y and Kojima K. Feasibility of laparoscopic gastrectomy for patients with poor physical status: a retrospective cohort study based on a nationwide registry database in Japan. Gastric Cancer 2020; 23: 310-318.

[37] Hiki N, Katai H, Mizusawa J, Nakamura K, Nakamori M, Yoshikawa T, Kojima K, Imamoto H, Ninomiya M, Kitano S and Terashima M; Stomach Cancer Study Group of Japan Clinical Oncology Group. Long-term outcomes of laparoscopy-assisted distal gastrectomy with suprapancreatic nodal dissection for clinical stage I gastric cancer: a multicenter phase II trial (JCOG0703). Gastric Cancer 2018; 21: 155-161.

[38] Ojima T, Nakamura M, Hayata K, Kitadani J, Katsuda M, Takeuchi A, Tominaga S, Nakai T, Nakamori M, Ohi M, Kusunoki M and Yamaue H. Short-term outcomes of robotic gastrectomy vs laparoscopic gastrectomy for patients with gastric cancer: a randomized clinical trial. JAMA Surg 2021; 156: 954-963.

[39] Nakauchi M, Suda K, Shibasaki S, Nakamura K, Kadoya S, Kikuchi K, Inaba K and Uyama I. Prognostic factors of minimally invasive surgery for gastric cancer: does robotic gastrectomy bring oncological benefit? World J Gastroenterol 2021; 27: 6659-6672.

[40] Seo HS, Shim JH, Jeon HM, Park CH and Song KY. Postoperative pancreatic fistula after robot distal gastrectomy. J Surg Res 2015; 194: 361-366.

[41] Guerra F, Giuliani G, Formisano G, Bianchi PP, Patriti A and Coratti A. Pancreatic complications after conventional laparoscopic radical gastrectomy versus robotic radical gastrectomy: systematic review and meta-analysis. J Laparoendosc Adv Surg Tech A 2018; 28: 1207-1215.