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Impact of Postoperative Complications on Recurrence in Patients With Stage II/III Gastric Cancer Who Received Adjuvant Chemotherapy With S-1

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Abstract. *Background: This study aimed to investigate the impact of postoperative complications (PCs) in patients with pathological stage (pStage) II or III gastric cancer (GC) who received adjuvant chemotherapy with S-1 after curative surgery. Patients and Methods: Altogether, data for 226 patients were examined retrospectively. The relationship between PCs and clinicopathological features and survival were examined. Results: Recurrence-free survival was significantly worse in the group with PCs than in the PC-negative group. On multivariate analysis, having PCs of grade 2 or more was an independent risk factor for recurrence (hazard ratio=1.721; 95% confidence intervaI=1.014-2.920; p=0.044). In addition, for each pStage analysis, having PCs of grade 2 or more was a risk factor for recurrence even in patients with pStage II GC. Conclusion: PC of grade 2 or more was an independent risk factor for recurrence in patients with pStage II GC who received adjuvant chemotherapy with S-1 after curative gastrectomy. Thus, for patients with PCs, even for those with pStage II GC, more effective adjuvant chemotherapy, such as S-1 plus docetaxel, may be needed.*

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Key Words: Gastric cancer, postoperative complication, recurrence, adjuvant chemotherapy.

Gastric cancer (GC) is the world's fifth most frequently diagnosed cancer and the third leading cause of cancer-related death in the world (1). Curative resection with D2 lymphadenectomy and postoperative adjuvant chemotherapy is the current standard treatment for stage II/III GC in East Asia (2-4). Furthermore, perioperative chemotherapy or chemoradiation therapy are recommended for clinical stage II/III GC in Europe and the United States (5-7). Postoperative adjuvant chemotherapy is believed to improve treatment outcomes by controlling cancer micrometastases that were not removed by surgery.

A number of reports demonstrated that postoperative complications (PCs) are associated with increased likelihood of disease recurrence in patients with GC and other malignancies (2, 8-27). While the specific mechanisms responsible for this relationship are not fully understood, several studies proposed that PCs suppress immune responses and induce proliferation of residual micrometastases, resulting in recurrence (11, 28-33). However, it is not currently known whether PCs affect disease recurrence in patients with advanced GC who received adjuvant postoperative chemotherapy after curative resection.

The aim of present study was to investigate the impact of PCs in patients with stage II/III GC who underwent postoperative adjuvant chemotherapy with S-1 after curative surgery.

Patients and Methods

Patients. This study was approved by the Ethics Committees of the Kanagawa Cancer Center before the study was initiated (approval

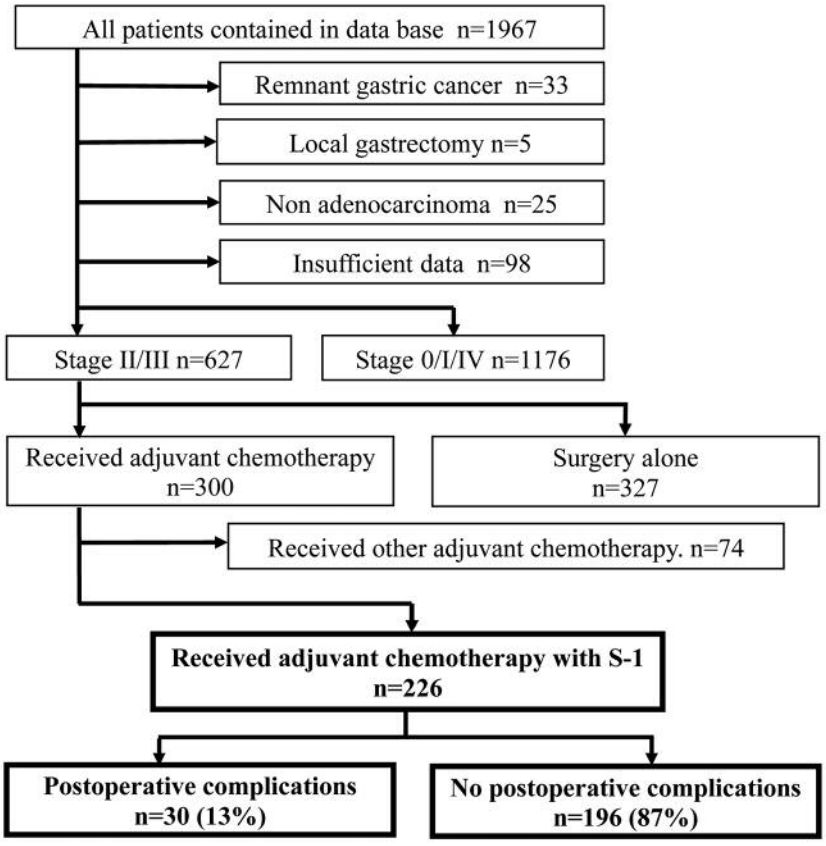


Figure 1. *Patient cohort of the present study. Altogether, 226 patients were assessed in this study, with 30 patients in the postoperative complication (PC) group and 196 patients in the non PC group.*

number: Epidemiological Study-99). Patients who underwent gastrectomy for GC between January 2000 and December 2011 at Kanagawa Cancer Center were identified from the clinical database. Patients that met the following inclusion criteria were investigated: i) History of curative resection for gastric cancer; ii) diagnosis of pathological stage (pStage) II/III gastric cancer; iii) history of adjuvant chemotherapy with S-1. Patients meeting the following criteria were excluded from analysis: i) Presence of remnant GC; ii) history of lymph node dissection below D1; and iii) specific types of GC.

Definition of postoperative complications. PC which occurred during hospitalization or within 30 days of surgery were retrospectively identified and classified (using the Clavien–Dindo classification) from the patients' medical records. The patients with PC of grade II or higher were classified into the PC group, while those without PC or with PC grade I or 0 were classified into the non PC group. Patients who experienced multiple complications were classified into the PC group.

Follow-up. In keeping with standard clinical care following GC after curative surgery, patient visits were performed every 3 months during the first 2 years following surgery and every 6 months from 2 to 5 years following surgery. Physical examinations, blood tests, and imaging (computed tomography scans, ultrasonography, or endoscopy) were performed to evaluate for recurrence of GC. When recurrence was suspected, additional imaging studies or diagnostic laparoscopy were performed.

Data collection. Clinical, surgical, and pathological data, and survival measured from surgery were collected from clinical databases and records. The classification of oncological features was based on the seventh edition of the International Union Against Cancer classification system (34). The extent of gastrectomy and lymphadenectomy were defined according to the Japanese Gastric Cancer Treatment Guidelines (35).

Statistical analyses. The relationship between the presence of PC and age was evaluated using the Mann–Whitney *U*-test. The relationship between the presence of PCs and clinicopathological features incorporated gender, American Society of Anesthesiologists score, tumor location, histological type, surgical procedure, TNM T-stage, TNM N-stage, and TNM M-stage for evaluation using Fisher's exact test and chi-squared test. The postoperative survival rate was analyzed by plotting the Kaplan–Meier graph, with differences in survival rates assessed using the log-rank test. A Cox proportional-hazards regression model was used for univariate and multivariate analyses. All statistical analyses were performed using

Table I. *Details of postoperative complications in patients with pathological stage II/III gastric cancer evaluated by Clavien-Dindo classification.*

Complication	Grade				
	II, n	III, n	IV, n	V, n	II-V, n (%)
Pancreatic fistula	6	1	0	0	7 (3.1)
Wound infection	6	1	0	0	7 (3.1)
Anastomotic stenosis	1	1	0	0	2 (0.9)
Ileus	1	1	0	0	2 (0.9)
Postoperative haemorrhage	1	1	0	0	2 (0.9)
Pneumonia	1	1	0	0	2 (0.9)
Heart failure	1	0	1	0	2 (0.9)
Delayed gastric emptying	0	1	0	0	1 (0.4)
Intraperitoneal abscess	1	0	0	0	1 (0.4)
Ascites	0	1	0	0	1 (0.4)
Liver dysfunction	1	0	0	0	1 (0.4)
Unknown origin infection	2	0	0	0	2 (0.9)
Total	21	8	1	0	30 (13.3)

EZR version 1.37 (Jichi University, Tochigi, Japan). Two-sided *p*-values were calculated, with differences considered significant value was less than 0.05.

Results

In total, 226 patients were assessed in this study. Thirty patients were classified into the PC group, while 196 patients were classified into the non PC group (Figure 1).

Details of PCs. PCs were observed in 13.3% (30/226) of all patients. Pancreatic fistula and wound infection were the most frequently observed, followed by anastomotic stenosis, ileus, pneumonia, and heart failure. Grade 2 PCs were observed in 9.3% (21/226) of patients, grade 3 in 3.5% (8/226), and grade 4 in 0.4% (1/226) (Table I).

The relationship between PCs and clinicopathological characteristics. Age was significantly higher in the non PC group compared to the PC group (p=0.033). In regards to the surgical procedure, the rate of total gastrectomy was significantly higher in the PC group than in the non PC group (p=0.031). No difference was observed in patient sex, American Society of Anesthesiologists score, tumor location, tumor depth, nodal involvement, TNM pathological stage, pathological type, and the extent of lymphadenectomy between the two groups (Table II).

Overall survival (OS). The median follow-up period was 52.5 months (range=5.4-130.3 months). No significant difference in OS was observed between the two groups (Figure 2A). In assessing OS in patients with stage II disease, the PC group exhibited worse OS than the non PC group (Figure 2B). No significant difference in OS was observed in patients with stage III disease between groups with and without PC (Figure 2C).

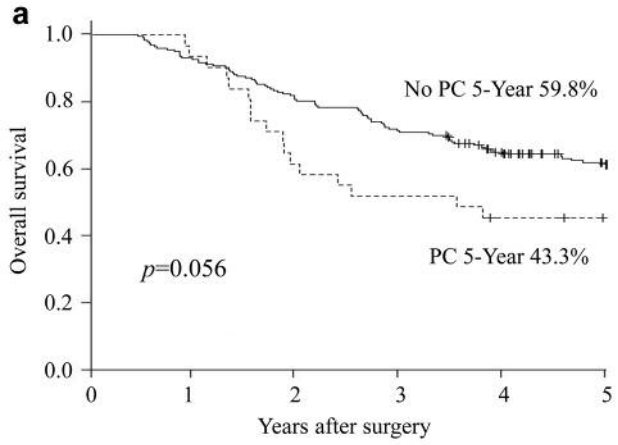
Table II. *The relationship between postoperative complications (PC) and clinicopathological characteristics.*

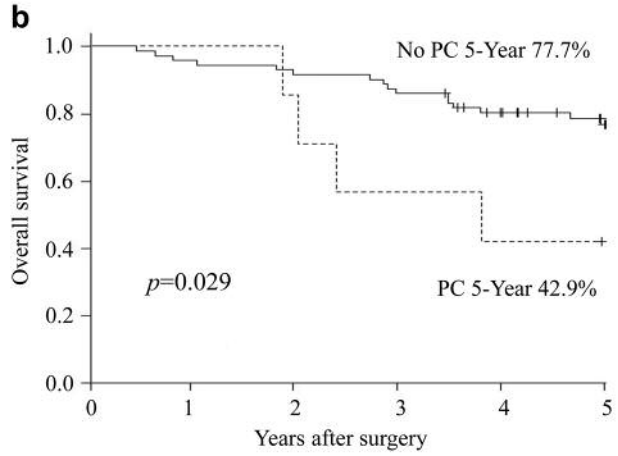
Characteristic	Non PC (n=196)	PC (n=30)	*p*-Value
Age, years			
Mean±SD	64±11.36	59±10.86	0.033
Gender, n			
Male	132	26	0.759
Female	64	4	
ASA score, n			
1	72	8	0.313
2/3	124	21	
Tumor location, n			
Lower third	58	8	0.311
Middle third	72	9	
Upper third	66	13	
Depth of invasion, n			
T1a/b	6	0	0.856
T2	28	3	
T3	42	6	
T4a/b	120	21	
Lymph node metastasis, n			
N0/1	65	12	0.536
N2/3	131	18	
pStage*, n			
II	72	7	0.217
III	124	23	
Histological type, n			
Intestinal	61	7	0.522
Diffuse	135	23	
Surgical procedure, n			
Proximal/distal gastrectomy	94	8	0.031
Total gastrectomy	102	22	
Extent of lymphadenectomy, n			
D1+	12	0	0.375
D2	184	30	

ASA score: American Society of Anesthesiologists score; pStage: pathological stage. *TNM seventh edition (34).

Recurrence-free survival (RFS). RFS was significantly longer in the non PC group than in the PC group (p=0.017) (Figure 3A). In evaluating RFS for individual pStages, RFS of the PC group was found to be significantly worse than that of the non PC group (Figure 3B) in patients with stage II disease. Conversely, no significant difference in RFS was observed between the PC and non PC groups in patients with stage III disease (Figure 3C).

Univariate and multivariate analyses of risk factors for recurrence. Univariate analyses demonstrated that total





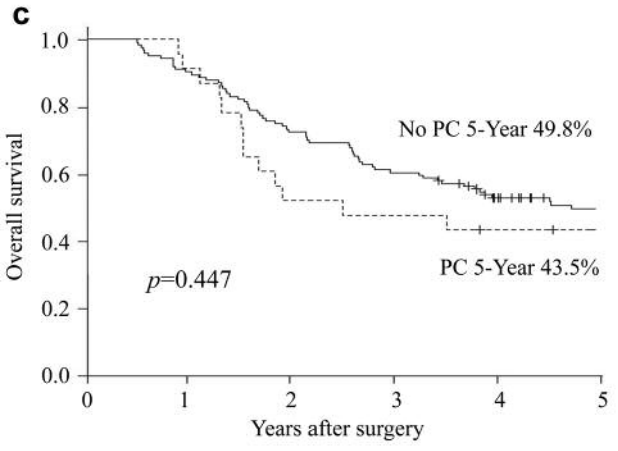
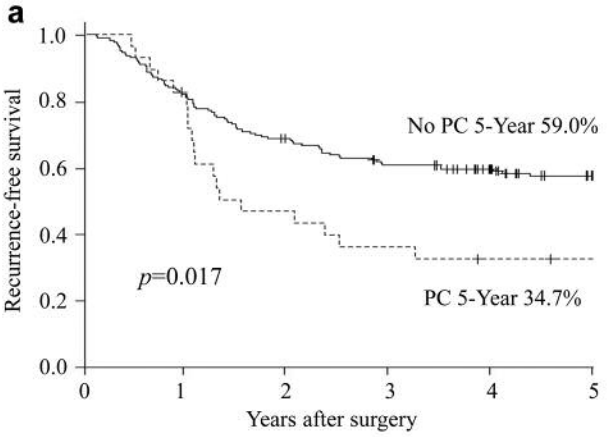
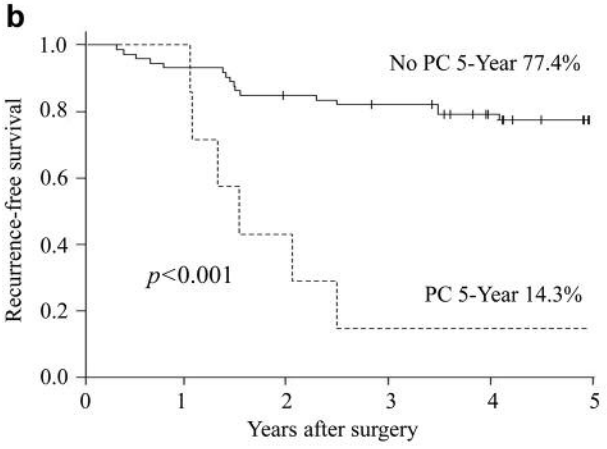


Figure 2. *Overall survival (OS) curves of the non postoperative complication (PC) and PC groups. The median follow-up period was 52.5 months (range=5.4-130.3 months). A: No significant difference in OS was observed between the groups in patients with stage II/III disease. B: In patients with stage II disease, the PC group exhibited significantly poorer OS compared to the non PC group. C: No significant difference in OS was observed between the groups in patients with stage III disease.*





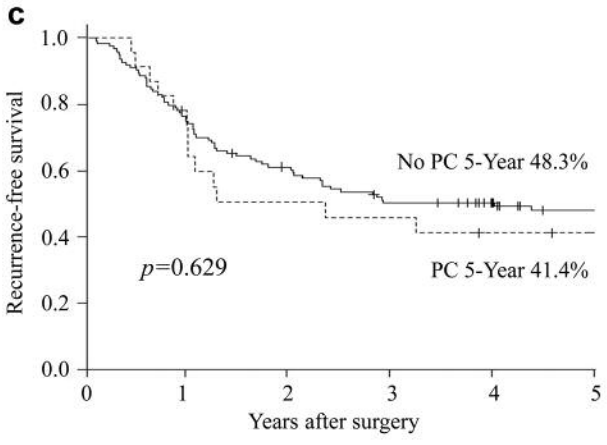


Figure 3. *Recurrence-free survival (RFS) curves of the non postoperative complication (PC) and PC groups. A: In patients with stage II/III disease, RFS was significantly poor in the PC group compared to the non PC group. B: In patients with stage II disease, RFS of the PC group was significantly poorer than that for the non PC group. C: Conversely, no significant difference in RFS was observed in patients with stage III disease between the two groups.*

Table III. *Univariate and multivariate analyses of recurrence-free survival in patients with pathological stage II/III gastric cancer.*

		Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age	≤74 Years	1			1		
	≥75 Years	1.264	0.740-2.157	0.391	1.441	0.815-2.546	0.209
Gender	Male	1			1		
	Female	1.299	0.862-1.958	0.211	1.512	0.984-2.323	0.059
ASA score	1	1			1		
	2/3	1.204	0.794-1.825	0.382	1.119	0.727-1.723	0.609
Histological type	Intestinal	1			1		
	Diffuse	1.277	0.822-1.985	0.277	1.178	0.744-1.863	0.485
Gastrectomy	Proximal/distal	1			1		
	Total	1.652	1.102-2.477	0.015	1.320	0.770-2.262	0.312
pStage*	II	1			1		
	III	2.321	1.457-3.698	<0.001	2.168	1.334-3.520	0.002
PC	Without	1			1		
	With	1.824	1.106-3.010	0.019	1.721	1.014-2.920	0.044

ASA score: American Society of Anesthesiologists score; CI: confidence interval; HR: hazard ratio; PC: Postoperative complications; pStage: pathological stage. *TNM seventh edition (34).

Table IV. *Univariate and multivariate analyses of recurrence-free survival in patients with pathologic stage II gastric cancer.*

		Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age	≤74 Years	1			1		
	≥75 Years	0.292	0.039-2.168	0.229	0.418	0.051-3.277	0.399
	Gender						
Gender	Male	1			1		
	Female	1.117	0.483-2.581	0.796	1.054	0.452-2.460	0.902
ASA score	1	1			1		
	2/3	1.741	0.686-4.417	0.243	1.167	0.418-3.259	0.768
Histological type	Intestinal	1			1		
	Diffuse	1.826	0.720-4.633	0.205	1.522	0.560-4.136	0.411
Gastrectomy	Proximal/distal	1			1		
	Total	2.166	0.947-4.952	0.067	0.637	0.090-4.504	0.651
PC	Without	1					
	With	6.277	2.401-16.410	<0.001	3.867	1.284-11.650	0.016

ASA score: American Society of Anesthesiologists score; CI: confidence interval; HR: hazard ratio; PC: Postoperative complications; pStage: pathological stage. *TNM seventh edition (34).

gastrectomy, pStage III, and PC were risk factors for recurrence. On multivariate analysis, pStage and PC were found to be independent risk factors for recurrence (Table III). Univariate and multivariate analyses performed for separate stages showed PC to be an independent risk factors for recurrence in patients with stage II disease (Table IV), while PC was not an independent risk factors for recurrence in stage III.

Initial recurrence site. Recurrence was observed in 101 out of 226 patients (44.7%). Peritoneal metastasis was the most frequent site of recurrence in both groups. Moreover, incidence of peritoneal metastases was significantly higher in the group with PC than in the non PC group (p=0.001; Table V).

Discussion

This study examined the effects of PCs on patients with stage II/III GC who received postoperative adjuvant chemotherapy with S-1 after curative surgery. In our study,

Table V. *Comparison of initial site of recurrence between groups with and without postoperative complications (PC).*

Recurrence	No PC (n=85)	PC (n=21)	*p*-Value
Peritoneal	35	14	0.001
Lymph node	22	5	0.372
Hematogenous	21	2	0.747
Local	6	0	0.718
Unknown	1	0	>0.99

having PCs was found to be an independent risk factor for recurrence when patients with stage II and III disease were combined, and when patients with stage II disease were considered separately.

Previous studies have shown that PCs after GC surgery increase the risk of disease recurrence. While the underlying pathophysiological processes have not been fully elucidated, two major mechanisms have been proposed based on previous reports. One possibility is that the systemic inflammatory response induced by PCs stimulates the proliferation of micrometastatic tumor cells remaining after surgery through inflammatory mediators (36, 37) such as interleukin-6 (38-40), nuclear factor-kappa B (41), and C-reactive protein (42). Another possibility is that the delay in the initiation of postoperative adjuvant chemotherapy due to PCs reduces the control of micrometastases remaining after surgery, resulting in disease proliferation (43).

Focusing on tumor cells remaining after surgery, patients with stage III GC can be considered to have more numerous micrometastatic sites than those with stage II disease. However, in assessing patients with disease of different pStages, patients of the PC group with stage II GC exhibited significantly worse OS and RFS than the non PC group. Similarly, multivariate analysis of those with stage II GC showed PCs to be an independent risk factor for disease recurrence. Conversely, no significant difference between the groups were observed for patients with stage III GC.

In elucidating the underlying mechanisms, we speculated that the lower number of micrometastatic tumor cells in patients with stage II disease may make the impact of PCs more evident, while the greater number of micrometastatic tumor cells in stage III disease may reduce their impact. Therefore, PCs have greater impact on recurrence in patients with stage II GC.

In past assessments of postoperative adjuvant chemotherapy for pStage III GC, the JACCRO-GC07 study demonstrated greater effectiveness of S-1 plus docetaxel than S-1 alone as adjuvant chemotherapy (3). Based on these findings, standard postoperative adjuvant chemotherapy for pStage III GC is currently S-1 plus docetaxel. Therefore, the most effective currently available treatment strategy for patients with pStage II GC with PC may be to administer S-1 plus docetaxel as postoperative adjuvant therapy.

This study has some limitations. Firstly, it was a single-institution retrospective study. Therefore, the current findings need to be confirmed in prospective trials. Secondly, evidence of the efficacy of adjuvant chemotherapy in patients with pStage II and III GC was not established between 2000 and 2005. While some patients received S-1, others received alternative regimens within clinical trials or within clinical practice. Therefore, there may be bias in the indication and the choice of S-1 adjuvant chemotherapy.

In conclusion, having PCs is an independent risk factor for recurrence in patients with pStage II GC receiving adjuvant S-1 chemotherapy after gastrectomy. Therefore, effective management of PCs in these patients would be to administer more effective adjuvant chemotherapy, such as combination chemotherapy with S-1 and docetaxel which is the standard treatment for pStage III GC.

Conflicts of Interest

All Authors have no conflicts of interest or financial ties to disclose.

Author's Contributions

Concept and study design were conducted by T. Hayashi, H. Watanabe and T. Oshima. Data collection and literature search were by H. Watanabe, K. Koumori, K. Hara, Y. Maezawa, K. Kano, Y. Shimoda, H. Fujikawa. Data analysis and interpretation were by H. Watanabe, T. Hayashi and T. Oshima. Interpretation of data was performed by all 21 investigators. Drafting of the article and figure preparation were by H. Watanabe, T. Hayashi and T. Oshima. Finally, this article was revised and approved by all 21 investigators. Thus, all Authors actively participated in this study.

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