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ORIGINAL ARTICLE

Impact of infectious complications on gastric cancer recurrence

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Abstract
Background Postoperative infectious complications increase disease recurrence in colorectal cancer patients. We herein investigated the impact of infectious complications on gastric cancer recurrence after curative surgery.
Methods In total, 502 patients who underwent R0 resection for gastric cancer were reviewed. Patients were classified into those with infectious complications (IC group) and those without infectious complications (NO group). The risk factors for recurrence-free survival (RFS) were identified.
Results Infectious complications, which occurred in 52 patients (10.4 %), included pneumonia, ileus with a systemic inflammatory reaction, anastomotic leakage, and intraperitoneal abscess. The overall 5-year RFS rate was 83 % in the NO group and 58 % in the IC group ($p = 0.000$). Multivariate analysis demonstrated that age, ASA score, stage, and infectious complications were significant predictors of RFS.
Conclusions Infectious complications were a risk factor for gastric cancer recurrence. To avoid causing infectious complications, the surgical procedure, surgical strategy, and perioperative care should be carefully planned.

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Introduction

Many previous studies [1–9] have demonstrated that the development of postoperative complications increased the risk of disease recurrence in various types of malignancies. Among surgical morbidities, infectious complications are the most frequent and directly related to surgery. Some authors [5, 9, 10] have suggested that the immunological response against postoperative infection enhanced the viability of undetectable residual tumor cells after surgery, thereby increasing disease recurrence.

However, despite these numerous studies, only three previous studies [7–9] demonstrated a correlation between infectious complications and poor survival in patients with gastric cancer. However, there were some drawbacks in these studies. Infectious complications were limited to only anastomotic and/or intraperitoneal abscess in two studies [7, 8], and patients who received postoperative chemotherapy were included in one study [9]. These differences could overestimate the relationships between infectious complication and survival.

The aim of the present study was to determine whether recurrence-free survival (RFS) would be shortened by any infectious complication of grade 2 or higher, as defined by the Clavien–Dindo classification [11], in patients who underwent curative resection for gastric cancer. In this study, all infectious complications were included, and the patients who received adjuvant chemotherapy were excluded.

Patients and methods

Patients

Patients were selected from the medical records of 733 consecutive patients who underwent gastrectomy for gastric adenocarcinoma at Kanagawa Cancer Centre from 2000 to 2005, according to the following criteria: (1) a pathologically common type of adenocarcinoma according to the Japanese Gastric Cancer Association (JGCA) guidelines [12] (special types, such as neuroendocrine tumors and adenosquamous carcinoma, were excluded); (2) patients without synchronous or metachronous (within 5 years before surgery) malignancies; and (3) those who had undergone curative resection (R0). Patients who received adjuvant chemotherapy or underwent limited gastrectomy with a less than D1 lymphadenectomy were excluded.

The extent of dissection was determined by the JGCA guidelines [12]. The resected specimens were examined histopathologically and staged according to the International Union Against Cancer (UICC) TNM 7th edition [13].

Definition of infectious complications

Complications of grades 2–5 according to the Clavien–Dindo classification that occurred during hospitalization and/or within 30 days after surgery were retrospectively determined from the patients' records [11]. Grade 1 complications were not evaluated to exclude the possibility of a description bias in the patient records. Infectious complications were defined as being present in patients who received antibiotic therapy for an infection or suspected infection and had at least one of the following: body temperature $\geq$38.0 °C and white blood cell count >10,000/μl. The patients were classified into those with infectious complications (IC group) and those without infectious complications (NO group).

Follow-up

Disease recurrence for T1N0 tumors was evaluated every 3 months during the first year and every 6 months thereafter for 4 years; for tumors $\geq$T2 or nodal disease, the recurrence was evaluated every 3 months during the first 2 years and every 6 months thereafter for 3 years. The oncological follow-up included physical examinations, blood tests, and abdominal computed tomographic scans or ultrasonography at 3- or 6-month intervals. When recurrence was suspected, additional imaging studies and/or laparoscopy were performed.

Statistical analysis

The SPSS version 12.0 software program (Statistical Package for the Social Sciences; SPSS, Chicago, IL, USA) was used to perform the statistical calculations. Between the IC and the NO groups, statistical comparisons of the differences in age were made using Student's t test, and all other comparisons were made by the chi-square test. The Kaplan–Meier method was used to calculate survival rates, and the log-rank test was used for comparisons of survival rates. RFS was defined as the period between surgery and the occurrence of an event, either disease recurrence or death, whichever came first. The data for patients who did not experience an event by the date of the final observation were treated as censored cases.

Uni- and multivariate Cox proportional hazards regression models were used to analyze the hazard ratios for RFS. Each cutoff value was set at the value where the hazard ratio was at its maximum. Variables with a probability value <0.05 in the univariate analysis were included in a subsequent multivariate analysis. Results with p values <0.05 were considered to be statistically significant.

Results

Clinicopathological characteristics

We selected 502 patients for this study. The clinicopathological characteristics are shown in Table 1. Age, American Society of Anesthesiology grade (ASA) score, tumor location, stage, pathological type, the procedure used to perform gastrectomy, and splenectomy were significantly different between the two groups. In the IC group, age tended to be higher, ASA score was greater, more proximal tumors were dominant, advanced stage was more frequent, and the patients received total gastrectomy and splenectomy more frequently than the NO group.

Among the 14 patients who were diagnosed with stage IV disease, 9 had resectable peritoneal metastasis, 4 had paraaortic lymph node metastasis, and 1 had liver metastasis. All 14 patients with stage IV were able to undergo curative resection. Most patients underwent D2 gastrectomy, but D1 was sometimes selected, especially when the tumor was confined to the mucosa and was a histologically differentiated type.

Infectious complications

Among the 502 patients, the overall mortality and morbidity rates, including infectious complications, were 0 % (0 patients) and 13.1 % (66 patients), respectively. The infectious complications included pneumonia, catheter-related sepsis, cholecystitis, enterocolitis, anastomotic

Table 1 Clinicopathological characteristics comparing between the NO group (those without infectious complications) and the IC group (those with infectious complications)

	NO group *N* (%)[a]	IC group *N* (%)[a]	Total *N* (%)[b]	*p* value[†]
Age (years old)				0.015
Mean ± SD	63 ± 10.29	66 ± 8.52	63 ± 10.16	
Median, range	64, 29–85	66, 42–81	64, 29–85	
Gender (M:F)				0.136
Male	327 (73)	43 (83)	370 (74)	
Female	123 (27)	9 (17)	132 (26)	
ASA score[c]				<0.001
1	234 (52)	13 (25)	247 (49)	
2	192 (43)	30 (58)	222 (44)	
3	24 (5)	9 (17)	33 (7)	
Tumor location				<0.001
Upper third	99 (22)	26 (50)	125 (25)	
Middle third	192 (43)	13 (25)	205 (41)	
Lower third	159 (35)	13 (25)	172 (34)	
Tumor depth[d]				0.257
T1a	150 (33)	10 (19)	160 (32)	
T1b	143 (32)	21 (40)	164 (33)	
T2	59 (13)	5 (10)	64 (13)	
T3	24 (5)	3 (6)	27 (5)	
T4a	65 (15)	11 (21)	76 (15)	
T4b	9 (2)	2 (4)	11 (2)	
Nodal involvement[d]				0.052
N0	331 (74)	31 (59)	362 (72)	
N1	52 (11)	5 (10)	57 (11)	
N2	27 (6)	8 (15)	35 (7)	
N3a	26 (6)	5 (10)	31 (6)	
N3b	14 (3)	3 (6)	17(4)	
Stage (TNM 7th)				0.002
I	317 (71)	33 (63)	350 (70)	
II	67 (15)	2 (4)	69 (14)	
III	56 (12)	13 (25)	69 (14)	
IV	10 (2)	4 (8)	14 (2)	
Pathological type				0.011
Diffuse type	192 (43)	11 (21)	203 (40)	
Intestinal type	226 (50)	36 (69)	262 (53)	
Mixed type	32 (7)	5 (10)	37 (7)	
Surgical procedure				0.002
Distal gastrectomy	296 (66)	21 (40)	317 (63)	
Proximal gastrectomy	4 (1)	1 (2)	5 (1)	
Total gastrectomy	150 (33)	30 (58)	180 (36)	
Extent of lymphadenectomy				0.241
D1	112 (25)	17 (33)	129 (26)	
D2	338 (75)	35 (67)	373 (74)	
Splenectomy				<0.001
No	428 (95)	40 (77)	468 (93)	
Yes	22 (5)	12 (23)	34 (7)	
Pancreatectomy				0.197
No	449 (99)	51 (98)	500 (99)	
Yes	1 (1)	1 (2)	2 (1)	

[a] Number of patients and percent (%) among each category in each group (except age)

[b] Number of patients and percent (%) in each category (except age)

[c] American Society of Anesthesiologists score

[d] Tumor depth and nodal involvement were based on TNM 7th edition

[†] Age was analyzed by Student's *t* test; other variables were analyzed by the chi-square test

Table 2 Details of postoperative infectious complications evaluated by Clavien–Dindo classification

	Grade 2	Grade 3	Grade 4	Grade 5	%
Pneumonia	19	0	2	0	4.1
Catheter-related sepsis	1	0	0	0	0.2
Cholecystitis	2	0	0	0	0.4
Enterocolitis	0	1	0	0	0.2
Anastomotic leakage	2	4	0	0	1.2
Pancreatic fistula	5	0	0	0	1.0
Wound infection	4	1	0	0	1.0
Ileus	2	5	0	0	1.4
Intraperitoneal abscess	2	4	0	0	1.2
Unknown origin	1	0	0	0	0.2
Any infectious complication	38	15	2	0	

Two infectious complications were observed in three patients: anastomotic leakage (grade 3) and wound infection (grade 3), pneumonia (grade 2) and wound infection (grade 2), and pancreatic fistula (grade 2) and wound infection (grade 2)

leakage, pancreatic fistula, wound infection, ileus with a systemic inflammatory reaction, and intraperitoneal abscess, which occurred in a total of 52 patients (10.4 %). The details are shown in Table 2. Pneumonia was the most frequently diagnosed complication, followed by ileus with a systemic inflammatory reaction, anastomotic leakage, and intraperitoneal abscess. Grade 2 complications occurred in 69 % of the patients, grade 3 in 27 % and grade 4 in 4 % of the patients. No mortality (grade 5) caused by infectious complications was observed. Infectious complications were observed in 33 patients with stage I, 2 with stage II, 13 with stage III, and 4 with stage IV disease.

Recurrence-free survival

The median follow-up period was 61 months (range, 1–110 months). The RFS curves are shown in Fig. 1a. There was a significant difference in the RFS between the NO and IC groups ($p < 0.000$). The 3-year RFS rates were 86 % and 64 %, and the 5-year RFS rates were 83 % and 58 %, in the NO and IC groups, respectively.

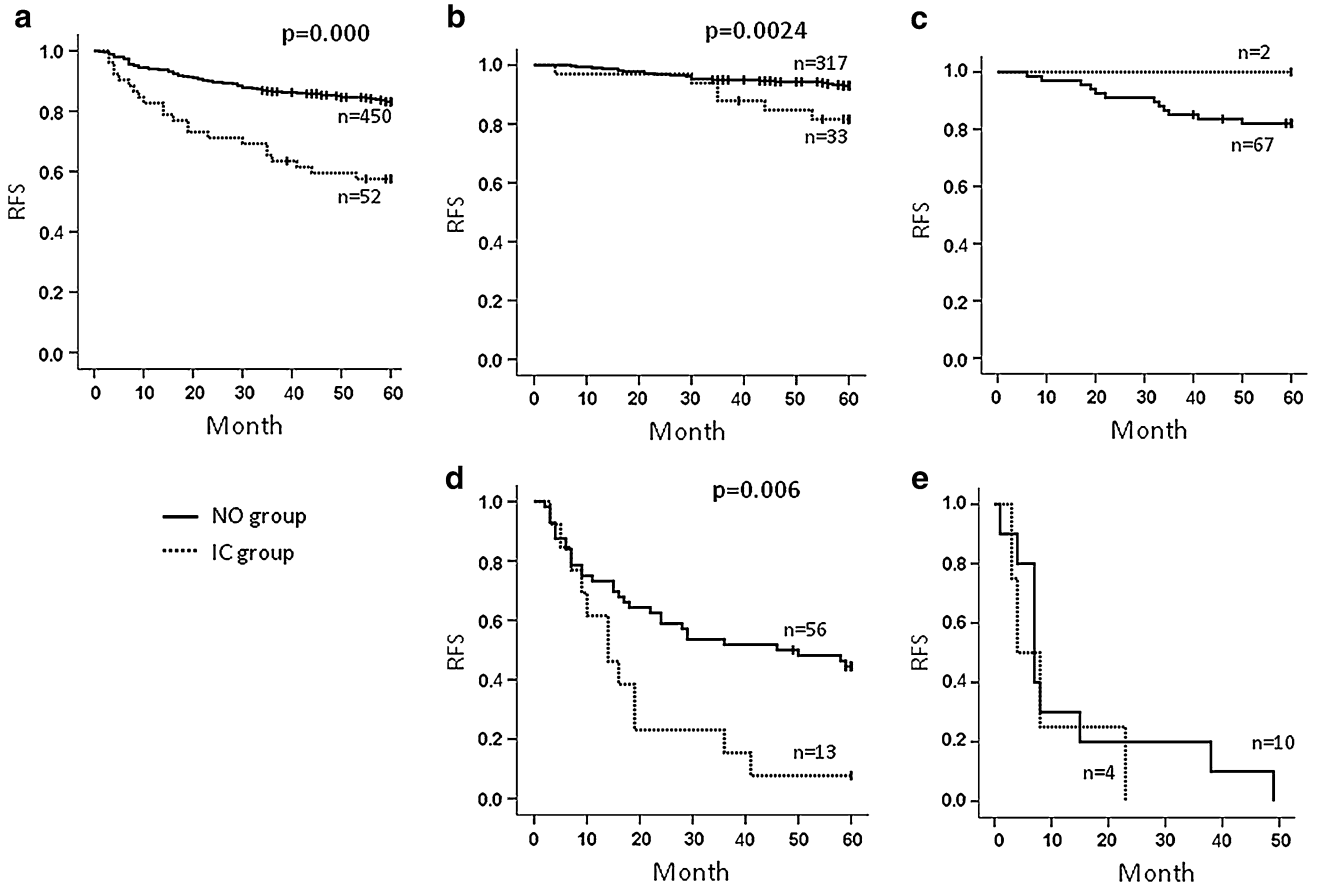

Fig. 1 Recurrence-free survival (RFS) curves of the NO group (those without infectious complications) and the IC group (those with infectious complications) in all patients (**a**), and in stage I (**b**), stage II (**c**), stage III (**d**), and stage IV (**e**) patients

Table 3 Results of univariate analysis for recurrence-free survival

	N	Hazard ratio	95 % CI	*p* value
Age (years)				
≤64	263	1	–	–
≥65	239	2.490	1.630–3.802	0.000
Gender				
Male	370	1	–	–
Female	132	1.21	0.948–1.565	0.109
ASA score[a]				
1	247	1	–	–
2	222	1.618	1.012–2.587	0.044
3	33	0.980	0.440–2.182	0.960
Tumor location				
M or L	377	1	–	–
U	125	2.395	1.598–3.591	0.000
Pathological type				
Intestinal type	262	1	–	–
Diffuse type	240	1.127	0.984–1.206	0.071
Extent of lymphadenectomy				
D1	129	1	–	
D2	373	2.384	1.329–4.275	0.004
Stage[b]				
I	350	1	–	–
II	69	2.267	1.153–4.458	0.018
III	69	12.390	7.677–19.996	0.000
IV	14	44.398	22.805–86.439	0.000
Splenectomy				
No	468	1	–	–
Yes	34	1.872	1.433–2.451	0.000
Infectious complication				
No	450	1	–	–
Yes	52	2.822	1.754–4.539	0.000

U upper third, *M* middle third, *L* lower third

[a] The American Society of Anesthesiologists score

[b] TNM 7th edition

Table 4 Results of multivariate analysis for recurrence-free survival

	Hazard ratio	95 % CI	*p* value
Age (years)			
≤64	1	–	–
≥65	1.998	1.226–3.154	0.003
ASA score[a]			
1	–	–	–
2	1.619	1.018–2.575	0.042
3	0.973	0.438–2.165	0.947
Tumor location			
M or L	1	–	–
U	1.308	0.832–2.046	0.241
Extent of lymphadenectomy			
D1	1	–	
D2	1.214	0.651–2.265	0.541
Stage[b]			
I	1	–	–
II	2.308	1.166–4.562	0.016
III	11.383	6.994–18.526	0.000
IV	39.025	19.092–79.771	0.000
Splenectomy			
No	1	–	–
Yes	1.087	0.583–2.027	0.794
Infectious complication			
No	1	–	–
Yes	1.958	1.154–3.289	0.013

U upper third, *M* middle third, *L* Lower third

[a] American Society of Anesthesiologists score

[b] TNM 7th edition

The RFS curves stratified by each disease stage are shown in Fig. 1b–e. The curves were clearly separated in patients with stage I and III cancers. The 3-year RFS rates of the NO and IC groups were 95 % and 88 % in stage I, 85 % and 100 % in stage II, 44 % and 15 % in stage III, and 20 % and 0 % in stage IV, respectively. In the patients with stage IV disease, the median duration of RFS was 7 months in the NO group and 4 months in the IC group.

Risk factors for recurrence

In the univariate analyses, age, ASA score, tumor location, extent of lymphadenectomy, stage, splenectomy, and infectious complications were all found to be significantly associated with RFS (Table 3). The multivariate analysis demonstrated that age, ASA score, stage, and infectious complications were all significant independent risk factors for the RFS (Table 4).

Initial recurrent site

The initial recurrent sites following gastrectomy are shown in Table 5. In the NO group, peritoneal metastasis was the most common recurrence, whereas lymph node metastasis was the most common in the IC group. The rate of lymph node recurrence was significantly higher in the IC group than in the NO group as determined by the chi-square test ($p = 0.043$).

Discussion

In the present study, we examined the relationships between infectious complications and survival in patients with gastric cancer. Previously, only three studies focused

Table 5 Comparison of initial recurrent site between NO group and IC group

	NO group $N = 75$	IC group $N = 22$	Total $N = 97$	p value*
Peritoneal metastasis	26	5	31	0.436
Liver metastasis	14	4	18	1.000
Lymph node metastasis	9	7	16	0.046
Lung metastasis	2	0	2	1.000
Local recurrence	2	1	3	0.542
Other	18	6	24	0.782
Unknown	8	1	9	0.679

* Chi-square test

on this issue [7–9]. One study was from Poland [7], and the authors only examined the relationship between anastomotic leakage and survival; no other infectious complications were included. The other two studies were from Japan [8, 9]. Tsujimoto et al. [9] reported a correlation between infectious complications and poor survival. However, they limited infectious complications to pneumonia, enterocolitis, cholecystitis, anastomotic leakage, and intraperitoneal abscess. Other infectious complications were excluded in their study. They also included the patients who received postoperative chemotherapy, which likely affected the results, because the prognosis is better in the patients who developed surgical complications and received adjuvant chemotherapy than in the patients who did not. Recently, Tokunaga et al. [8] reported a correlation between intraabdominal infectious complications and poor survival. They excluded patients who received adjuvant chemotherapy. However, they limited infectious complications to anastomotic leakage and intraabdominal abscess; all other infectious complications were excluded. Pneumonia is one of the major complications after gastrectomy; it is known to cause systemic inflammation and affect host immune response, and should therefore be included in any analysis of the impact of infectious complications on the patient survival. Based on these, we reevaluated the relationships between all infectious complications defined as grade 2 or higher and survival in patients who did not receive adjuvant chemotherapy.

Our findings clearly indicated that infectious complications were an independent risk factor for disease recurrence in patients who had undergone curative gastrectomy for gastric cancer. One possible reason for this association is that the patients who developed infectious complications may have had some factor(s) that led to decreased host immunity against the tumor. After reviewing studies of mouse models, Dunn et al. [14] suggested that the adaptive immune system could function by identifying and eliminating nascent tumor cells. A second possible reason is that the patients who developed infectious complications had some factor(s) that enhanced the growth of micrometastatic tumor cells that remained after surgery. The mediators released because of the infectious complications could work to enhance the migration and invasion of malignant cells, leading to metastasis [15].

In the subset analyses, a very large difference in RFS between the groups was observed in stage III patients. The 3-year RFS was 44 % in the NO group but only 15 % in the IC group. A significant difference in the RFS was observed even in stage I patients. The 3-year RFS rate was 95 % in the NO group and 88 % in the IC group. However, there was no significant difference in RFS between the NO and IC groups among stage IV patients, although the median RFS rates were slightly different, which could be explained as follows. First, there was a possibility that a difference does exist but did not reach statistical significance in this study because of the small sample size. Second, because the number of tumor cells in stage IV patients was likely to be much higher in comparison to that of the other patients with early-stage disease, a detectable tumor was more likely to be detected sooner in these patients regardless of whether there was an infection.

In the present study, lymph node recurrence was more frequently observed in the IC group than in the NO group. When comparing the nodal involvement of the background between the two groups, the proportions of pN3 and stage III were higher in the IC group than the NO group, which partially explains the difference in nodal recurrence. Another possibility is that the presence of residual cancer cells in the lymph nodes could be affected by the infection or inflammatory response or both. In patients with colorectal cancer, Mirnezami et al. [4] reported that anastomotic leakage enhanced only the local recurrence, but not distant metastasis, and they assumed that the local inflammatory response contributes to local recurrence. In gastric cancer, however, the mechanism underlying the differences in the recurrence patterns caused by infectious complications was unclear.

This study had several potential limitations. First, this was a retrospective study. Complications were recorded from the patients' records. Most treatments were selected by the individual physicians, not based on a specific protocol. Second, the study included a time bias. The postoperative management was changed between 2000 and 2005. In addition, the duration of fasting after surgery was shortened in 2002, which may have affected host immunity and complications. Third, there was a selection bias in the population. During the period from 2000 to 2005, evidence for the efficacy of adjuvant chemotherapy in stage II and III patients had not yet been established. Some patients received S-1, whereas some received other oral fluoropyrimidines or taxanes in clinical trials or clinical practice.

Physicians may have initiated adjuvant chemotherapy for patients who had sufficient organ function, but not for the patients who developed infectious complications. It is also possible that physicians may have started chemotherapy only for the patients who had advanced disease, but not for those who had early disease. As there was a huge bias in the indications for and selection of adjuvant chemotherapy, we excluded patients who received adjuvant chemotherapy from the analyses in this study. Thus, the population in this study was inversely selected. Fourth, the patients did not receive S-1 adjuvant chemotherapy, which is now the standard of care after surgery for stage II/III patients in Japan. Further clarification is needed to determine whether infectious complications are related to a poor survival when adjuvant chemotherapy is given. Fifth, the number of patients with stage II disease was small, and only two of these patients developed infectious complications. Therefore, a statistical comparison in stage II patients was not possible. Considering these limitations, the present findings should be confirmed with data obtained from a prospective trial in which patients receive modern cytotoxic/immunological therapy.

In conclusion, infectious complications were a risk factor for disease recurrence in patients who underwent curative surgery for gastric cancer. To avoid infectious complications, the surgical procedure, perioperative care, and the surgical strategy, such as the extent of dissection or combined organ resection, should be carefully planned. Our results need to be confirmed in a prospective trial using the current standard of care.

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