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RESEARCH

Prognostic Impact of Post-operative Infectious Complications in Gastric Cancer Patients Receiving Neoadjuvant Chemotherapy: Post Hoc Analysis of a Randomized Controlled Trial, JCOG0501

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Abstract

Purpose Post-operative infectious complication (IC) is a well-known negative prognostic factor, while showing neoadjuvant chemotherapy (NAC) may cancel out the negative influence of IC. This analysis compared the clinical impacts of IC according to the presence or absence of NAC in gastric cancer patients enrolled in the phase III clinical trial (JCOG0501) which compared upfront surgery (arm A) and NAC followed by surgery (arm B) in type 4 and large type 3 gastric cancer.

Methods The subjects were 224 patients who underwent R0 resection out of 316 patients enrolled in JCOG0501. The prognoses of the patients with or without ICs in each arm were investigated by univariable and multivariable Cox regression analyses.

Results There were 21 (20.0%) IC occurrences in arm A and 15 (12.6%) in arm B. In arm A, the overall survival (OS) of patients with ICs was slightly worse than those without IC (3-year OS, 57.1% in patients with ICs, 79.8% in those without ICs; adjusted hazard ratio (95% confidence interval), 1.292 (0.655–2.546)). In arm B, patients with ICs showed a trend of better survival than those without ICs (3-year OS, 80.0% in patients with IC, 74.0% in those without IC; adjusted hazard ratio, 0.573 (0.226–1.456)).

Conclusion This study could not indicate the negative prognostic influence of ICs in gastric cancer patients receiving NAC, which might be canceled by NAC. To build exact evidence, further investigation with prospective and large numbers of data might be expected.

Keywords Gastric cancer · Neoadjuvant chemotherapy · Postoperative complication

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Introduction

Gastric cancer is the sixth most common cancer and the fifth leading cause of cancer death worldwide [1]. Surgical resection is necessary for the cure of gastric cancer, but it sometimes causes surgical morbidities. In addition, many researchers from all over the world have reported that postoperative infectious complication (IC) deteriorates the prognosis of patients with various malignant tumors including gastric cancer [2–14]. However, the precise mechanism of this negative prognostic influence caused by ICs is still unclear. Some reports explain it by delay of initiating adjuvant therapy and by activation of microscopic residual tumors due to cytokines induced by ICs [15, 16].

In contrast, recent reports from not only Asian countries but also Western countries have shown intriguing results that neoadjuvant chemotherapy (NAC) would cancel out the negative influence of postoperative ICs on survival [17–20]. However, all these reports are single-center, retrospective studies. Therefore, it is expected that the prognostic influence of IC can be compared in randomized cohorts with and without NAC of a prospective multicenter study.

Japan Clinical Oncology Group conducted a phase III study (JCOG0501) comparing upfront surgery and NAC followed by surgery for type 4 and large type 3 gastric cancer to investigate the superiority of NAC, resulting in no difference in overall survival between the two treatment arms [21]. At the moment, only JCOG0501 can provide prospective and large sample data which can investigate the association between the prognostic influence of ICs and NAC in Japan. Moreover, it is difficult to collect data in Western countries to investigate the prognostic association because peri-operative chemotherapy is established as a standard treatment. The aim of this study is to explore whether NAC can cancel out the negative prognostic influence of ICs using the data of JCOG0501.

Materials and Methods

Patients

In JCOG0501, enrolled patients were randomly assigned to receive upfront surgery followed by post-operative adjuvant S-1 chemotherapy (arm A) or to receive NAC with S-1 and cisplatin (CDDP) followed by D2 gastrectomy and post-operative adjuvant S-1 chemotherapy (arm B). The detailed inclusion and exclusion criteria of JCOG0501 were reported previously [21]. The key eligibility criteria were (1) histologically proven adenocarcinoma of the stomach, (2) Bormann type 4 or large (≥ 8 cm) type 3, (3) no evidence of distant metastasis, (4) an age of 20–75 years, (5) no previous treatment for any malignancy, and (6) obtained written informed consent. Histological assessment of the tumors and tumor regression grade achieved by NAC was performed according to the Japanese Classification of Gastric Carcinoma (2nd English edition) [22]. The protocol defined that adjuvant chemotherapy must be initiated within 6 weeks after surgery, that initiation within 12 weeks is allowed as the protocol treatment in case of morbidity, and that the protocol treatment is terminated in case adjuvant chemotherapy is not initiated within 12 weeks.

This post hoc analysis included exclusively patients who underwent R0 resection to precisely evaluate the prognostic influence of infectious complications.

Definition of Post-operative Infectious Complications

In JCOG0501, all complications were diagnosed by clinical findings and assessed by each physician prospectively. The severity of postoperative ICs was evaluated according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) [23]. In this post hoc study, grade 2 or more complications of anastomotic leakage, pancreatic fistula, abdominal abscess, intrathoracic abscess, wound infection, and pneumonia were defined as ICs. Patients in each treatment arm were divided into two groups according to the presence (IC group) or absence (non-IC group) of IC. This study collected not only infectious complications which we included as ICs in this study but also other complications such as paralytic ileus, gastrointestinal occlusion, atelectasis, and non-infectious surgical site complications.

Statistical Analysis

Overall survival (OS) was defined by the time from the date of surgery until death from any cause, or censored at the final follow-up of surviving patients. Progression-free survival (PFS) was defined as the time from the date of surgery until the first recurrence or death from any cause, or censored at the final follow-up from patients surviving without recurrence. OS and PFS were calculated by the Kaplan–Meier method and compared by the log-rank test. A two-sided p-value of less than 0.05 was considered to be significant.

Hazard ratios and their 95% confidence interval between IC and non-IC were estimated using the Cox regression model. To adjust the patients' background, multivariable Cox regression analysis using the backward elimination method based on the criterion of $\alpha = 0.3$ was performed, and the adjusted hazard ratio (HR) was calculated. All statistical

analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patients' Characteristics

From 17 October 2005 to 19 July 2013, 316 patients from 44 hospitals were enrolled in JCOG0501 and were randomly assigned to arm A or arm B. The CONSORT diagram is demonstrated in Fig. 1. The subjects of this post hoc analysis were 224 patients: 105 patients in arm A and 119 patients in arm B for whom R0 resection was performed. Among these 224 patients (36 in the IC group and 188 in the non-IC group), 36 (21 in arm A and 15 in arm B) developed grade 2 or more ICs, anastomotic leakage in 4 patients (4 in arm A and 0 in arm B), pancreatic fistula in 20 (13 in arm A and 7 in arm B), abdominal abscess in 12 (6 in arm A and 6 in arm B), wound infection in 3 (2 in arm A and 1 in arm B), and pneumonia in 4 (3 in arm A and 1 in arm B).

Table 1 shows patients' characteristics in this study's population according to the occurrence of ICs. All patients in the IC group of arm B underwent total gastrectomy. Combined organ resection was performed in 165 (87.8%) of the non-IC group and in 33 (91.7%) of the IC group. Combined resection was performed as follows: the spleen in 178 patients (85 in arm A and 93 in arm B), gall bladder in 80 (40 in arm A and 40 in arm B), pancreas in 17 (8 in arm A and 9 in arm B), colon in 7 (3 in arm A and 4 in arm B), adrenal gland in 3 (1 in arm A and 2 in arm B), liver in 2 (2 in arm A and 0 in arm B), diaphragm in 2 (2 in arm A and 0 in arm B), and other organs in 6 (5 in arm A and 1 in arm B). In arm B, tumor regression grade 3 (pathological Complete Response) was observed in 3 cases (2.9%) of the non-IC group but in none of the IC group. The final stage was stage IA in 8 (2 in arm A and 6 in arm B), stage IB in 31 (6 in arm A and 25 in arm B), stage II in 59 (19 in arm A and 40 in arm B), stage IIIA in 54 (31 in arm A and 23 in arm B), stage IIIB in 45 (29 in arm A and 16 in arm B), and stage IV in 24 (18 in arm A and 6 in arm B).

In arm A, 72 (85.7%) patients of the non-IC group and 13 (61.9%) of the IC group received adjuvant chemotherapy. In arm B, 90 (86.5%) patients of the non-IC group and 14 (93.3%) of the IC group did. The details of ICs are indicated in Table 2 describing the numbers of ICs shown by complication grades.

Overall Survival Between Non-IC and IC Groups in Arm A (Upfront Surgery Group) and Arm B (Neoadjuvant Group)

Figure 2 shows the OS of non-IC and IC groups in arms A and B. In arm A, the 3-year and 5-year OS were 79.8% and 64.2% in the non-IC group and 57.1% and 47.6% in the IC group, respectively. Survival of the IC group was worse than the non-IC group, although not significantly (unadjusted hazard ratio (HR) = 1.545, 95% confidential interval (CI) 0.806–2.960, log-rank p-value = 0.1863). In arm B, the 3-year and 5-year OS were 74.0% and 61.0% in the non-IC group and 80.0% and 73.3% in the IC group, respectively. Survival of the IC group was slightly better than in the non-IC group in arm B (unadjusted HR = 0.644, 95% CI 0.257–1.614, log-rank p-value = 0.3440) (Table 3).

Table 3 summarizes unadjusted and adjusted HRs in each analysis. In arm A analyses, age, tumor type, cT, cN,

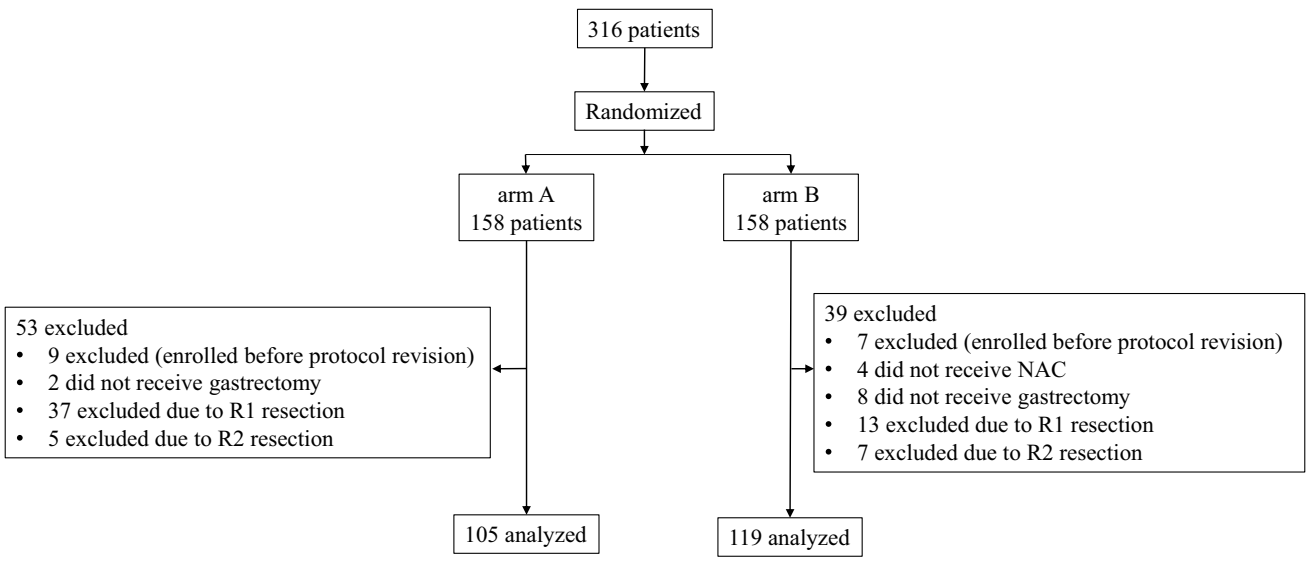

Fig. 1 The CONSORT diagram

Table 1 Patient characteristics

	Arm A		Arm B		Total	
	Non-IC	IC	Non-IC	IC	Non-IC	IC
	84	21	104	15	188	36
Age, median (range)	62 (29–75)	63 (39–75)	64 (35–75)	64 (30–72)	63 (29–75)	63 (30–75)
Gender						
Male	53 (63.1%)	15 (71.4%)	59 (56.7%)	14 (93.3%)	112 (59.6%)	29 (80.6%)
Female	31 (36.9%)	6 (28.6%)	45 (43.3%)	1 (6.7%)	76 (40.4%)	7 (19.4%)
PS						
0	82 (97.6%)	19 (90.5%)	103 (99.0%)	15 (100%)	185 (98.4%)	34 (94.4%)
1	2 (2.4%)	2 (9.5%)	1 (1.0%)	0	3 (1.6%)	2 (5.6%)
Tumor type						
Type 3	41 (48.8%)	10 (47.6%)	44 (42.3%)	7 (46.7%)	85 (45.2%)	17 (47.2%)
Type 4	43 (51.2%)	11 (52.4%)	60 (57.7%)	8 (53.3%)	103 (54.8%)	19 (52.8%)
cT						
cT1	0	0	0	0	0	0
cT2	12 (14.3%)	7 (33.3%)	13 (12.5%)	3 (20.0)	25 (13.3%)	10 (27.8%)
cT3	70 (83.3%)	13 (61.9%)	89 (85.6%)	11 (73.3%)	159 (84.6%)	24 (66.7%)
cT4	2 (2.4%)	1 (4.8%)	2 (1.9%)	1 (6.7%)	4 (2.1%)	2 (5.6%)
cN						
cN0	31 (36.9%)	8 (38.1%)	42 (40.4%)	6 (40.0%)	73 (38.8%)	14 (38.9%)
cN1	35 (41.7%)	7 (33.3%)	44 (42.3%)	7 (46.7%)	79 (42.0%)	14 (38.9%)
cN2	18 (21.4%)	6 (28.6%)	18 (17.3%)	2 (13.3%)	36 (19.1%)	8 (22.2%)
cStage						
cStage I	5 (6.0%)	4 (19.0%)	5 (4.8%)	1 (6.7%)	10 (5.3%)	5 (13.9%)
cStage II	31 (37.0%)	5 (23.8%)	39 (37.5%)	6 (40.0%)	70 (37.2%)	11 (30.6%)
cStage III	46 (54.8%)	11 (52.4%)	42 (40.4%)	6 (40.0%)	88 (46.8%)	17 (47.2%)
cStage IV	2 (2.4%)	1 (4.8%)	18 (17.3%)	2 (13.3%)	20 (10.6%)	3 (8.3%)
Surgery time, median	252	297	245	315	246.5	297.5
Blood loss, median	395	750	445	510	407.5	632.5
Surgical procedure						
Distal gastrectomy	17 (20.2%)	2 (9.5%)	14 (13.5%)	0	31 (16.5%)	2 (5.6%)
Total gastrectomy	67 (79.8%)	19 (90.5%)	90 (86.5%)	15 (100%)	157 (83.5%)	34 (94.4%)
Combined resection						
No	11 (13.1%)	1 (4.8%)	12 (11.5%)	2 (13.3%)	23 (12.2%)	3 (8.3%)
Yes	73 (86.9%)	20 (95.2%)	92 (88.5%)	13 (86.7%)	165 (87.8%)	33 (91.7%)
Pancreas	7 (8.3%)	1 (4.8%)	7 (6.7%)	2 (15.4%)	14 (7.4%)	3 (8.3%)
Spleen	66 (78.6%)	19 (90.5%)	80 (76.9%)	13 (86.7%)	146 (77.7%)	32 (88.9%)
Adrenal gland	1 (1.2%)	0	1 (1.0%)	1 (7.7%)	2 (1.1%)	1 (2.8%)
Colon	3 (3.6)	0	3 (2.9%)	1 (7.7%)	6 (3.2%)	1 (2.8%)
Gallbladder	31 (36.9%)	9 (42.9%)	34 (32.7%)	6 (46.2%)	65 (34.6%)	15 (41.7%)
Liver	2 (2.4%)	0	0	0	2 (1.1%)	0
Diaphragm	1 (1.2%)	1 (4.8%)	0	0	1 (0.5%)	1 (2.8%)
Other	5 (6.0%)	0	1 (1.0%)	0	6 (3.2%)	0
pT						
M	1 (1.2%)	0	3 (2.9%)	1 (6.7%)	4 (2.1%)	1 (2.8%)
SM	0	1 (4.8%)	2 (1.9%)	1 (6.7%)	2 (1.1%)	2 (5.6%)
MP	3 (3.6%)	0	13 (12.5%)	1 (6.7%)	16 (8.5%)	1 (2.8%)
SS	17 (20.2%)	7 (33.3%)	41 (39.4%)	4 (26.7%)	58 (30.9%)	11 (30.6%)
SE	57 (67.9%)	10 (47.6%)	39 (37.5%)	6 (46.2%)	96 (51.1%)	16 (44.4%)
SI	6 (7.1%)	3 (14.3%)	3 (2.9%)	2 (13.3%)	9 (4.8%)	5 (13.9%)

Table 1 (continued)

	Arm A		Arm B		Total	
	Non-IC	IC	Non-IC	IC	Non-IC	IC
	84	21	104	15	188	36
pN						
pN0	13 (15.5%)	5 (23.8%)	45 (43.3%)	6 (46.2%)	58 (30.9%)	11 (30.6%)
pN1	28 (33.3%)	7 (33.3%)	34 (32.7%)	6 (46.2%)	62 (33.0%)	13 (36.1%)
pN2	36 (42.9%)	5 (23.8%)	22 (21.2%)	3 (20.0%)	58 (30.9%)	8 (22.2%)
pN3	7 (8.3%)	4 (19.0%)	3 (2.9%)	0	10 (5.3%)	4 (11.1%)
Peritoneal dissemination						
pP0	81 (96.4%)	19 (90.5%)	103 (99.0%)	15 (100%)	184 (97.9%)	34 (94.4%)
pP+	3 (3.6%)	2 (9.5%)	1 (1.0%)	0	4 (2.1%)	2 (5.6%)
Cytology						
pCY0	84 (100%)	21 (100%)	104 (100%)	15 (100%)	188 (100%)	36 (100%)
pCY1	0	0	0	0	0	0
Final stage						
I A	1 (1.2%)	1 (4.8%)	4 (3.8%)	2 (13.3%)	5 (2.7%)	3 (8.3%)
I B	4 (4.8%)	2 (9.5%)	23 (22.1%)	2 (13.3%)	27 (14.4%)	4 (11.1%)
II	15 (17.9%)	4 (19.0%)	36 (34.6%)	4 (26.7%)	51 (27.1%)	8 (22.2%)
III A	27 (32.1%)	4 (19.0%)	19 (18.3%)	4 (26.7%)	46 (24.5%)	8 (22.2%)
III B	26 (31.0%)	3 (14.3%)	14 (13.5%)	2 (13.3%)	40 (21.3%)	5 (13.9%)
IV	11 (13.1%)	7 (33.3%)	5 (4.8%)	1 (6.7%)	16 (8.5%)	8 (22.2%)
Complete response (grade 3)	0	0	3 (2.6%)	0	3 (1.6%)	0
Tumor regression grade						
Grade 0			12 (11.5%)	1 (6.7%)		
Grade 1a			29 (27.9%)	5 (33.3%)		
Grade 1b			22 (21.2%)	4 (26.7%)		
Grade 2			38 (36.5%)	5 (33.3%)		
Grade 3			3 (2.9%)	0		
Adjuvant chemotherapy						
Yes	72 (85.7%)	13 (61.9%)	90 (86.5%)	14 (93.3%)	162 (86.2%)	27 (75.0%)
No	12 (14.3%)	8 (38.1%)	14 (13.5%)	1 (6.7%)	26 (13.8%)	7 (19.4%)

IC infectious complication

pStage, adjuvant chemotherapy, pT, pN, and peritoneal dissemination were used as covariates, and the backward elimination method extracted pStage, adjuvant chemotherapy, pT, and pN. Multivariable analysis comparing the IC with the non-IC showed adjusted HR as 1.292 (95% CI 0.655–2.546, $p = 0.4601$). In arm B analyses, covariates were age, tumor type, cT, cN, pStage, tumor regression grade, adjuvant chemotherapy, pT, pN, and peritoneal dissemination. The backward elimination method extracted tumor type, cT, tumor regression grade, pT, pN, and peritoneal dissemination. Adjusted HR was 0.573 (95% CI = 0.226–1.456, $p = 0.242$). The p-value for the interaction of IC between arm A and arm B was 0.121 which was not obviously significantly different.

Progression-Free Survival Between Non-IC and IC Groups in Arm A and Arm B

Figure 3 shows the PFS of non-IC and IC groups in arm A and arm B. In arm A, the PFS of IC group was slightly inferior to the non-IC (3-year PFS of IC vs. non-IC is 57.1% vs. 61.9%) (unadjusted HR = 1.264, 95% CI 0.667–2.397, log-rank p-value = 0.4714). In arm B, the PFS of the IC group was apparently better than the non-IC group (3-year PFS is 73.3% in the IC group vs. 58.7% in the non-IC group) (unadjusted HR = 0.526, 95% CI 0.211–1.310, log-rank p-value = 0.1606) (Table 3).

In multivariable analysis using the backward elimination method, extracted covariates were the same between OS and PFS analyses. Adjusted HR was 1.075 (95%

Table 2 Detail of infectious complications

	Arm A	Arm B
Grade 2 infectious complications	16	8
Anastomotic leakage	2 (12.5%)	0
Pancreatic fistula	11 (68.8%)	4 (50.0%)
Abdominal abscess	1 (6.3%)	1 (12.5%)
Intrathoracic abscess	0	0
Wound infection	1 (6.3%)	1 (12.5%)
Pneumonia	1 (6.3%)	2 (25.0%)
Grades 3–4 infectious complications	11	9
Anastomotic leakage	1 (9.1%)	0
Pancreatic fistula	2 (18.2%)	3 (33.3%)
Abdominal abscess	5 (45.5%)	5 (55.6%)
Intrathoracic abscess	1 (9.1%)	0
Wound infection	1 (9.1%)	0
Pneumonia	1 (9.1%)	1 (11.1%)
Total of number of cases with infectious complications grade 2 or more	21	15

CI = 0.553–2.087, $p = 0.8319$) in arm A, and adjusted HR was 0.454 (95% CI = 0.180–1.143, $p = 0.0937$) in arm B.

Discussion

This is the first report that investigated whether the negative prognostic influence of IC might be canceled out by neoadjuvant chemotherapy, using data from a randomized phase III study comparing upfront surgery and NAC in gastric cancer patients. Interestingly, the prognostic impacts of IC were apparently different between the upfront surgery and NAC arms. In the upfront surgery arm, the OS of the IC group was slightly inferior to that of the non-IC group, while the survival of the IC group tended to be superior to that of the non-IC group in the NAC arm. It is suggested that NAC may somehow change the negative prognostic influence of IC in type 4 and large type 3 gastric cancer, although there is no reasonable explanation of the favorable prognostic impacts of IC. Previous reports showing the prophylactic effect of NAC canceling negative prognostic impacts of IC are all retrospective single-center studies using non-randomized cohorts [17, 18, 20]. Even though the present study could not confirm the prophylactic effect, this is the first study that used randomized and prospective data, showing the importance of further investigation of this issue.

In the upfront surgery arm of this study, the OS curve of the IC group was slightly inferior to that of the non-IC group; however, a statistical difference was not observed. The difference in PFS between IC and non-IC groups was slightly smaller than that in OS. Although many studies have shown the negative prognostic influence of ICs [2–9, 15] due to postoperative inflammation, immunosuppression, delay of adjuvant therapy, or sepsis which can cause growth of residual tumors leading to poor prognosis [15, 16, 24–27], arm A of this study did not show the significant negative influence on type 4 and large type 3 gastric cancer. The most plausible reasons why this data did not show the negative effect of ICs are as follows. First, the sample size and the number of this cohort were not so large. Previous reports included approximately 700–1000 cases in total which had 40–200 incidences of complications, while this study had only 274 cases in total which included 43 incidences of ICs. A greater number of cases could have clarified the prognostic difference between the IC and non-IC groups. Second, many previous reports investigated the negative influence of severe complications, while this study focused on grade 2 or more ICs. Moderate complications like grade 2 might not have a large risk of deteriorating oncological prognosis. However,

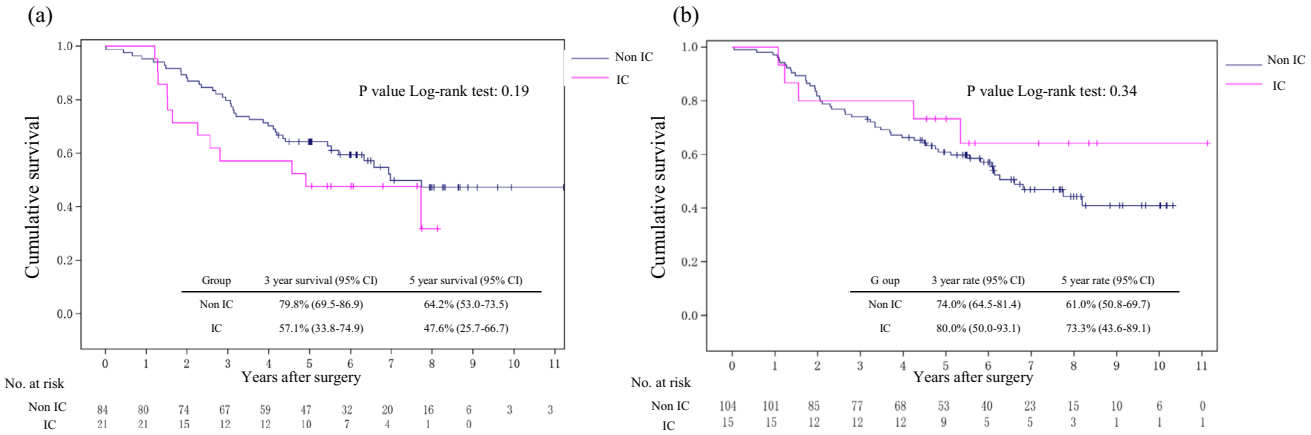

Fig. 2 Overall survival between the non-IC and IC groups of arm A (**a**) and arm B (**b**) with the Kaplan–Meier Method

Table 3 Hazard ratio of each survival analysis

	Unadjusted			Adjusted		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
OS in arm A						
Non-IC	1			1		
IC	1.545	0.806–2.960	0.19	1.292	0.655–2.546	0.46
OS in arm B						
Non-IC	1			1		
IC	0.644	0.257–1.614	0.35	0.573	0.226–1.456	0.24
PFS in arm A						
Non-IC	1			1		
IC	1.264	0.667–2.397	0.47	1.075	0.553–2.087	0.83
PFS in arm B						
Non-IC	1			1		
IC	0.526	0.211–1.310	0.17	0.454	0.180–1.143	0.09

IC infectious complication, *HR* hazard ratio

analysis focusing on severe complications in this study would be too vague to provide precise analysis due to the far too small number of events.

This post hoc analysis showed another intriguing data, that is, the IC rate of arm B is smaller than arm A. We presume that this difference mainly came from downstaging obtained by NAC, namely, tumor shrinkage can reduce the risk of unnecessary organ injury that could reduce the incidence of IC. Studies comparing upfront surgery and NAC in gastric cancer have reported that the IC rate in the NAC group was equal to or smaller than that in the upfront surgery group [20, 28–30]. Lowering the incidence of IC can be one benefit of NAC. Some researchers speculate that NAC could reduce the number of residual tumors whose growth might be stimulated by ICs and that this may lead to a reduction of the negative influence of ICs. Besides, other researchers believe that NAC might decrease immune response after surgery even in patients with IC, which eventually mitigates the growth of residual tumors.

In this study, the association of IC with prognosis is different between arms A and B. Only from this result, it seems as if IC could have favorable impacts on the prognosis. However, such a theory is hardly acceptable because there are no plausible reasons. In this study, we presume that a high adjuvant therapy rate could play a certain role in improving the prognosis in the IC group in arm B, as the proportion of patients receiving adjuvant chemotherapy was higher in the IC group (93.3%) compared to that of the non-IC group (86.5%) in arm B. However, the exact reasons are still unclear.

This study has several limitations. First, this study targeted only type 4 and large type 3 gastric cancer which require total gastrectomy in most cases. It is concerning that the result of this study might not be generalized in other macroscopic types. Second, the total number was

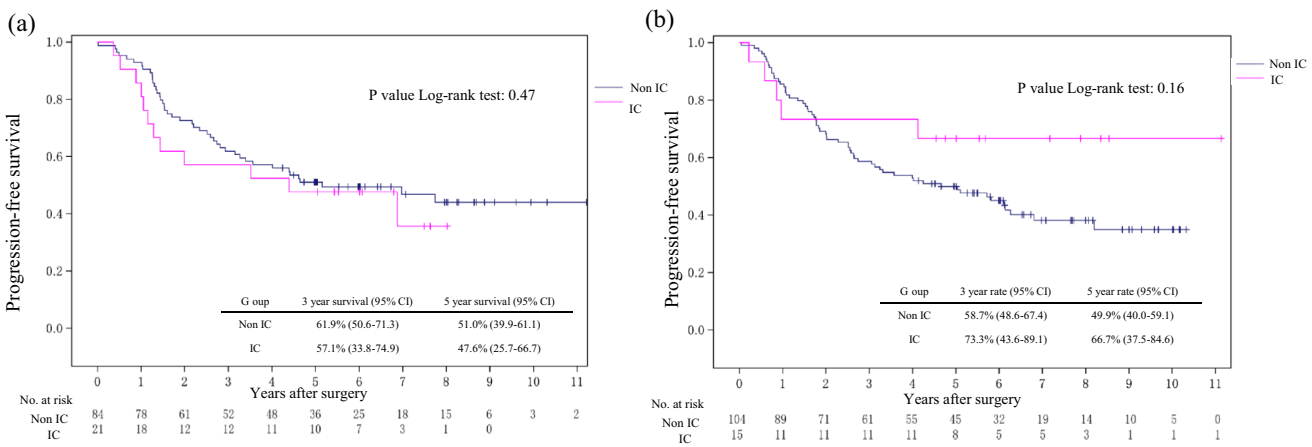

Fig. 3 PFS between the non-IC and IC groups of arm A (**a**) and arm B (**b**) with the Kaplan–Meier method

not large enough to precisely investigate the prognostic impact of ICs. To confirm our hypothesis that the negative prognostic impact of ICs is canceled out by NAC, we need a larger number of events in the large phase III study. Now, in the JCOG stomach cancer study group, a large phase III study, JCOG1509, comparing NAC followed by surgery and adjuvant chemotherapy and upfront surgery followed by adjuvant chemotherapy is ongoing. We will perform a post hoc analysis using the cohort of JCOG1509. Third, although the study population with strict criteria between arm A and arm B was randomized, it cannot guarantee clinical discrepancies between IC and non-IC groups in each arm. Finally, this study's complication rate was very low [31], undermining accurate statistical analysis. Complication rates in other reports showing the prophylactic effect of NAC were 28–50% [17, 18, 20], which are clearly different from ours and should be considered. Therefore, it is warranted to perform a study of a large sample size to confirm the negative prognostic effect of ICs and the prophylactic effect of NAC.

In conclusion, the present study did not show the significant negative influence of ICs in gastric cancer patients receiving NAC, which might be canceled by NAC. Further investigation with large sample data is expected to confirm these prognostic effects.

Author Contribution MH, TY, MS, NB, and MT contributed to conceptualization, methodology, writing—original draft, and writing—review and editing. JM contributed to formal analysis, investigation, resources, data curation, and writing—review and editing. SH, YK, YI, HI, and YC contributed to resources, data curation, and writing—review and editing.

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Data Availability The datasets generated during and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethical Approval The study protocol of JCOG0501 was approved by the JCOG Protocol Review Committee and the institutional review board of each participating hospital before the initiation of JCOG0501, and was performed in accordance with the international ethical recommendations stated in the Declaration of Helsinki and the Japanese Ethical Guidelines for Clinical Research. Informed consent including the secondary use of the collected data was obtained from the patients before enrollment. JCOG0501 was registered with UMIN-CTR, number C000000279.

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Competing Interests TY reports personal fees from MSD, BMS, Ono, Taiho, Eli Lilly, Chugai, Pfizer, Nihon Kayaku, TERUMO, Covidien, and Johnson & Johnson outside the submitted work. JM reports personal fees from Chugai Pharmaceutical and Taiho Pharmaceutical outside the submitted work, and his spouse is an employee of Pfizer. MS reports personal fees from Taiho Pharmaceutical during the study period. YC reports lecture fees from Ono Pharmaceutical and Bristol Myers Squibb Company. NB received a research grant from Ono and Takeda and honorarium from Taiho, Ono, Daiichi-Sankyo, and Bristol-Myers Squibb outside the submitted work. MT reports personal fees from Taiho Pharmaceutical, Chugai Pharmaceutical, Ono Pharmaceutical, Bristol-Myers Squibb, Yakult Honsha, Takeda Pharmaceutical, Eli Lilly Japan KK, Pfizer Pharmaceutical Japan, Daiichi Sankyo, Johnson and Johnson KK, Medtronic Japan, Intuitive Japan, and Olympus outside the submitted work. All other authors declare that there is no conflict of interest directly relevant to the content of this manuscript.

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