Prognostic impact of infectious complications: exploratory analysis of JCOG0501 phase III trial.

Masato Hayashi, Junki Mizusawa, Shinji Hato, Yoshiaki Iwasaki, Mitsuru Sasako, Yasuyuki Kawachi, Hiroyasu Iishi, Yasuhiro Choda, Narikazu Boku, Takaki Yoshikawa, Masanori Terashima

Stomach Cancer Study Group of Japan Clinical Oncology Group (JCOG), Japan

Correspondence to: Dr. Takaki Yoshikawa; E-mail: tayoshik@ncc.go.jp

JCOG Japan Clinical Oncology Group (www.jcog.jp/en/)

453

Backgrounds

- ✓ Postoperative infectious complication (IC) reportedly causes poor prognosis in patients with various malignant tumors including gastric cancer.
- ✓ Recent reports revealed that neoadjuvant chemotherapy (NAC) would cancel out the negative effect of postoperative ICs.
- ✓ Moreover, there was a report that postoperative ICs were associated with a worse prognosis only in non-responders, not in responders.
- ✓ However, all these reports are from single-center, retrospective studies.
- ✓ Randomized phase III trial JCOG0501 compared primary surgery followed by adjuvant S-1 (arm A) with neoadjuvant chemotherapy with S-1/CDDP followed by surgery and adjuvant S-1 (arm B) in type 4 and large type 3 gastric cancer, but the trial could not show survival superiority of arm B to arm A.

Aim

The aim of this study is to investigate the prognostic association between NAC and ICs in gastric cancer by using the data of JCOG0501.

Key eligibility criteria of JCOG0501

(1) Histologically proven adenocarcinoma of the stomach
(2) Borrmann type 4 or large (≥ 8 cm) type 3
(3) no evidence of distant metastasis
(4) no involvement of the esophagus > 3 cm
(5) age of 20–75 years
(6) Eastern Cooperative Oncology Group performance status of 0 or 1
(7) no previous chemotherapy or radiotherapy for any malignancy
(8) no previous surgery for GC excluding endoscopic mucosal resection or endoscopic submucosal dissection
(9) no prominent bleeding or gastrointestinal stenosis
(10) sufficient oral intake
(11) adequate organ function

Study design and CONSORT diagram

Study design of JCOG 0501

Type 4/large type 3 gastric cancer, P0CY0, P0CY1, P1CY0, P1CY1, cM0, cH0, cN0-2, PS 0-1, 20-75 y.o

Randomization

Adjustment factors
- Institution
- Tumor type (3/4)
- Depth of invasion (T1-3/4)
- Lymph node (N0/N1/N2)

Arm A: Primary Surgery arm (N=158)
D2 gastrectomy + adjuvant chemotherapy (8 course of S-1)

16 excluded
- 9 excluded (enrolled before protocol revision)
- 2 did not receive gastrectomy
- 5 excluded due to R2 resection

142 analyzed

IC group of Arm A (N=28)

VS

Non-IC group of Arm A (N=114)

Arm B: NAC arm (N=158)
NAC (2 course of S-1 with CDDP)+D2 gastrectomy + adjuvant chemotherapy (8 course of S-1)

26 excluded
- 7 excluded (enrolled before protocol revision)
- 4 did not receive NAC
- 8 did not receive gastrectomy
- 7 excluded due to R2 resection

132 analyzed

*This study compared the prognosis between Non IC group and IC group.

IC group of Arm B (N=15)

VS

Non-IC group of Arm B (N=117)

- ✓ OS and RFS were compared between Non-IC group and IC group of arm B.
- ✓ OS and RFS were compared between Non-IC group and IC group of arm A.

Endpoints & Statistical methods

Primary endpoint:
- Overall survival (OS) of Non-IC group and IC group of arm B (NAC group)

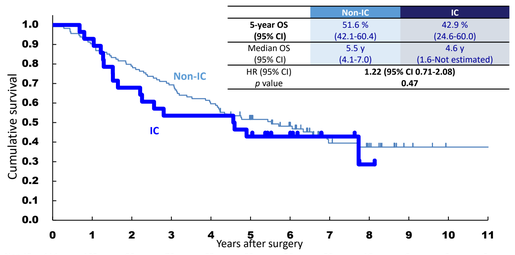
Secondary endpoints:
- Relapse-free survival (RFS) of Non-IC group and IC group of arm B (NAC group)
- OS and RFS of Non-IC group and IC group of arm A (Primary surgery group)

Statistical analysis
OS and RFS were calculated by Kaplan Meier method. In addition, univariable analysis for OS and RFS was performed using Cox proportional hazard model.

Definition of infectious complications
Grade 2 or more anastomotic leakage, pancreatic fistula, abdominal abscess, intrathoracic abscess, surgical site infection, and pneumonia were evaluated by CTCAE v3.0 and were defined as infectious complications.

Overall survival and Relapse-free survival in Arm A (Primary surgery group) (n=142)

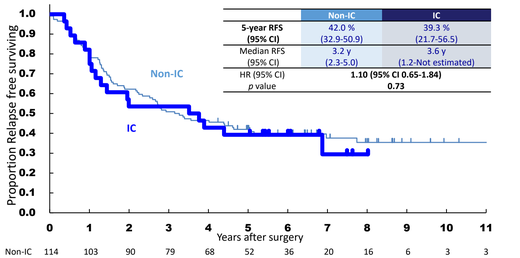
OS of Non-IC group and IC group of arm A population analyzed with Kaplan Meier Methods.



	Non-IC	IC
5-year OS (95% CI)	51.6 % (42.1-60.4)	42.9 % (24.6-60.0)
Median OS (95% CI)	5.5 y (4.1-7.0)	4.6 y (1.6-Not estimated)
HR (95% CI)	1.22 (95% CI 0.71-2.08)	
p value	0.47	

	0	1	2	3	4	5	6	7	8	9	10	11
Non-IC	114	103	90	79	68	52	36	20	16	6	3	3
IC	28	26	19	15	15	12	8	4	1	0	0	0

RFS of Non-IC group and IC group of arm A population analyzed with Kaplan Meier Methods.

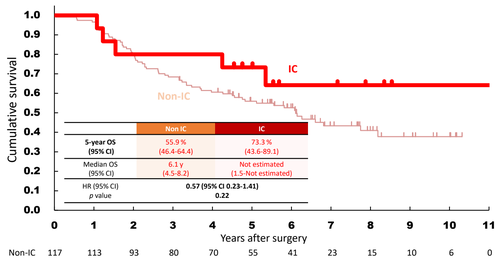


	Non-IC	IC
5-year RFS (95% CI)	42.0 % (32.9-50.9)	39.3 % (21.7-56.5)
Median RFS (95% CI)	3.2 y (2.3-5.0)	3.6 y (1.2-Not estimated)
HR (95% CI)	1.10 (95% CI 0.65-1.84)	
p value	0.73	

	0	1	2	3	4	5	6	7	8	9	10	11
Non-IC	114	103	90	79	68	52	36	20	16	6	3	3
IC	28	26	19	15	15	12	8	4	1	0	0	0

Overall survival and Relapse-free survival in Arm B (NAC group) (n=132)

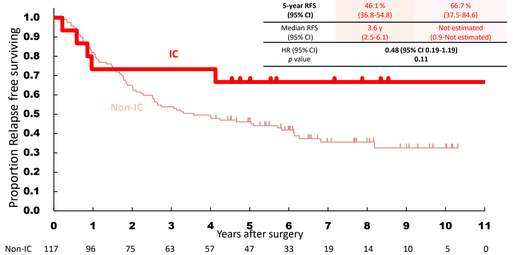
OS of Non-IC group and IC group of arm B population analyzed with Kaplan Meier Methods.



	Non IC	IC
5-year OS (95% CI)	55.9 % (46.4-64.4)	73.3 % (43.6-89.1)
Median OS (95% CI)	6.1 y (4.5-8.2)	Not estimated (1.5-Not estimated)
HR (95% CI)	0.57 (95% CI 0.23-1.41)	
p value	0.22	

	0	1	2	3	4	5	6	7	8	9	10	11
Non-IC	117	113	93	80	70	55	41	23	15	10	6	0
IC	15	15	12	12	12	9	5	5	3	1	1	1

RFS of Non-IC group and IC group of arm B population analyzed with Kaplan Meier Methods.



	Non IC	IC
5-year RFS (95% CI)	46.1 % (36.8-54.8)	66.7 % (37.5-84.6)
Median RFS (95% CI)	3.6 y (2.5-6.1)	Not estimated (0.9-Not estimated)
HR (95% CI)	0.48 (95% CI 0.19-1.19)	
p value	0.11	

	0	1	2	3	4	5	6	7	8	9	10	11
Non-IC	117	96	75	63	57	47	33	19	14	10	5	0
IC	15	11	11	11	11	8	5	5	3	1	1	1

Summary

- ✓ Infectious complications were observed in 28 (19.7%) in arm A and 15 (11.4%) in arm B.
- ✓ The OS of arm A was 69.3% in Non-IC group and 53.6% in IC group at 3-years and was 51.6% in Non-IC group and 42.9% in IC group at 5-years (HR 1.220, 95% CI [0.714-2.084], p=0.4671)
- ✓ The OS of arm B was 68.4% in Non-IC group and 80.0% in IC group at 3-years and was 55.9% in Non-IC group and 73.3% in IC group at 5-years (HR 0.567, 95% CI [0.228-1.412], p=0.2229).
- ✓ In the subset analyses, this upsetting by infectious complications was evident in type 4 (HR 1.043 in arm A and HR 0.386 in arm B).
- ✓ Infectious complications did not worsen the OS in JCOG0501, especially in patients who had type 4 and received NAC before surgery.

Conclusions

- ✓ Infectious complications did not worsen the OS in either Arm A or Arm B of JCOG0501.

Acknowledgement

Participating Institutions (44 institutions)

- ✓ Hakodate Goryokaku Hospital
- ✓ Iwate Medical University
- ✓ National Hospital Organization, Sendai Medical Center
- ✓ Miyagi Cancer Center
- ✓ Yamagata Prefectural Central Hospital
- ✓ Tochigi Cancer Center
- ✓ National Defense Medical College
- ✓ Saitama Cancer Center
- ✓ National Cancer Center Hospital East
- ✓ National Cancer Center Hospital
- ✓ Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital
- ✓ Tokyo Medical and Dental University Hospital
- ✓ Cancer Institute Hospital of Japanese Foundation for Cancer Research
- ✓ Toranomon Hospital
- ✓ Tokyo Metropolitan Bokutoh Hospital
- ✓ Kanagawa Cancer Center
- ✓ Niigata Cancer Center Hospital
- ✓ Nagaoka Chuo General Hospital
- ✓ Tsubame Rosai Hospital
- ✓ Toyama Prefectural Central Hospital
- ✓ Gifu Municipal Hospital
- ✓ Shizuoka General Hospital
- ✓ Shizuoka Cancer Center
- ✓ Aichi Cancer Center Hospital
- ✓ National Hospital Organization Kyoto Medical Center
- ✓ Kyoto Second Red Cross Hospital
- ✓ Osaka University Graduate School of Medicine
- ✓ Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases
- ✓ Osaka National Hospital
- ✓ Osaka Medical College
- ✓ Toyonaka Municipal Hospital
- ✓ Sakai Municipal Hospital
- ✓ Kobe University Graduate School of Medicine
- ✓ Hyogo College of Medicine
- ✓ Hyogo Cancer Center
- ✓ Itami City Hospital
- ✓ Tenri Hospital
- ✓ Wakayama Medical University, School of Medicine
- ✓ Shimane University Faculty of Medicine
- ✓ Hiroshima City Hospital
- ✓ Hiroshima City Asa Hospital
- ✓ Fukuyama City Hospital
- ✓ National Hospital Organization Shikoku Cancer Center
- ✓ Kochi Health Sciences Center

The study was supported in part by the National Cancer Center Research and Development Funds (23-A-19, 26-A-4, 29-A-3, 2020-J-3), the Grant-in-Aid for Clinical Cancer Research (H19-015, H22-027, H22-23) from the Ministry of Health, Labour and Welfare of Japan. The authors are grateful to the members of the JCOG Data Center and JCOG Operations Office for their support in this study.

Conflicts of Interest to declare

The first presenting author, Masato Hayashi, has no financial conflicts of interest to disclose concerning the presentation.

Patient characteristics

		Non IC			IC		
	N	Arm A 114	Arm B 117	Total 231	Arm A 28	Arm B 15	Total 43
Age	Median (range)	62 (29-75)	64 (35-75)	63 (29-75)	63 (39-75)	64 (30-72)	63 (30-75)
Sex	Male	69 (60.5%)	66 (56.4%)	135 (58.4%)	17 (60.7%)	14 (93.3%)	31 (72.1%)
	Female	45 (39.5%)	51 (43.6%)	96 (41.6%)	11 (39.3%)	1 (6.7%)	12 (27.9%)
ECOG PS	0	109 (95.6%)	116 (99.1%)	225 (97.4%)	25 (89.3%)	15 (100%)	40 (93.0%)
	1	5 (4.4%)	1 (0.9%)	6 (2.6%)	3 (10.7%)	0	3 (7.0%)
Tumor Type	Type 3	46 (40.1%)	46 (39.3%)	92 (39.8%)	11 (39.3%)	7 (46.7%)	18 (41.9%)
	Type 4	68 (59.9%)	71 (60.7%)	139 (60.2%)	17 (60.7%)	8 (53.3%)	25 (58.1%)
Blood loss	Median (range)	400 (40-2233)	395 (65-1950)	400 (40-2233)	673 (220-2600)	510 (154-4320)	600 (154-4320)
Surgery	Distal/ Total gastrectomy	18 (15.8%)/ 96 (84.2%)	15 (12.8%)/ 102 (87.2%)	33 (14.3%)/ 198 (85.7%)	2 (7.1%)/ 26 (92.9%)	0/ 15 (100%)	2 (4.7%)/ 41 (95.3%)
pT	T1-2/ T3-4	4 (3.5%)/110 (96.5%)	18 (6.8%)/ 96 (82.1%)	22 (9.5%)/ 206 (89.2%)	1 (3.6%)/27 (96.4%)	3 (20.0%)/12 (80.0%)	4 (9.3%)/39 (90.7%)
pN	N0/N1/N2/N3	14 (12.3%)/ 36 (31.6%) 54 (47.4%)/ 10 (8.8%)	49 (41.9%)/ 37 (31.6%) 28 (23.9%)/ 3 (2.6%)	63 (27.3%)/ 73 (31.6%) 82 (35.5%)/ 13 (5.6%)	5 (17.9%)/ 7 (25.0%) 11 (39.3%)/ 5 (17.9%)	6 (46.2%)/ 6 (46.2%) 3 (20.0%)/ 0	11 (25.6%)/ 13 (30.2%) 14 (32.6%)/ 5 (11.6%)
pStage	I / II / III / IV	5 (4.4%)/ 15 (13.2%)/ 56 (49.1%)/ 38 (33.3%)	27 (23.1%)/ 36 (30.8%)/ 34 (29.1%)/ 17 (14.5%)	32 (13.9%)/ 51 (22.1%)/ 90 (39.1%)/ 55 (23.8%)	3 (10.7%)/ 4 (14.3%)/ 10 (35.7%)/ 11 (39.3%)	4 (26.7%)/ 4 (26.7%)/ 6 (40.0%)/ 1 (6.7%)	7 (16.3%)/ 8 (18.6%)/ 16 (37.2%)/ 12 (27.9%)
Tumor Regression Grade	0 / 1a/ 1b/ 2/ 3		13 (11.1%)/ 34 (29.1%) 25 (21.4%)/42 (35.9%)/ 3 (2.6%)			1 (6.7%)/ 5 (33.3%) 4 (26.7%)/5 (33.3%)/ 0	

Subgroup Analysis in arm A (Primary surgery group)

			Univariable analysis for OS			
Factor	Category	Group	Event/N	3y OS (95% CI)	HR (95% CI)	p value
Age	≤ 64	Non-IC	38/70	70 (57.8-79.3)	1	
		IC	9/15	66.7 (37.5-84.6)	1.177(0.568-2.438)	0.6607
	≥ 65	Non-IC	26/44	68.2 (52.3-79.8)	1	
		IC	8/13	38.5(14.1-62.8)	1.276(0.575-2.830)	0.5491
Tumor type	type 3	Non-IC	19/46	78.3(63.4-87.7)	1	
		IC	6/11	54.4(22.9-78.0)	1.625(0.645-4.096)	0.3033
	type 4	Non-IC	45/68	63.2(50.6-73.4)	1	
		IC	11/17	52.9(27.6-73.0)	1.043(0.539-2.019)	0.9006
pStage	I-III	Non-IC	33/76	82.9(72.4-89.7)	1	
		IC	7/17	70.6(43.1-86.6)	1.042(0.460-2.356)	0.9222
	IV	Non-IC	31/38	42.1(26.4-57.0)	1	
		IC	10/11	27.3(6.5-53.9)	1.252(0.611-2.568)	0.5394
Adjuvant chemotherapy	No	Non-IC	18/24	45.8(25.6-64.0)	1	
		IC	8/12	50.0(20.8-73.6)	0.896(0.385-2.085)	0.7984
	Yes	Non-IC	46/90	75.6(65.3-83.2)	1	
		IC	9/16	56.3(29.5-76.2)	1.203(0.588-2.460)	0.6123

Subgroup Analysis in arm B (NAC group)

			Univariable analysis for OS			
Factor	Category	Group	Event/N	3y OS (95% CI)	HR (95% CI)	p value
Age	≤ 64	Non-IC	33/63	66.7 (53.6-76.8)	1	
		IC	3/8	87.5 (38.7-98.1)	0.654 (0.200-2.137)	0.4824
	≥ 65	Non-IC	29/54	70.4 (56.3-80.7)	1	
		IC	2/7	71.4 (25.8-92.0)	0.490 (0.117-2.063)	0.3310
Tumor type	type 3	Non-IC	20/46	76.1 (61.0-86.0)	1	
		IC	3/7	85.7 (33.4-97.9)	0.903 (0.268-3.044)	0.8696
	type 4	Non-IC	42/71	63.4 (51.1-73.4)	1	
		IC	2/8	75.0 (31.5-93.1)	0.386 (0.093-1.595)	0.1884
ypStage	I-III	Non-IC	49/100	74.0 (64.2-81.5)	1	
		IC	4/14	85.7 (53.9-96.2)	0.519 (0.187-1.439)	0.2074
	IV	Non-IC	13/17	35.3 (14.5-57.0)	1	
		IC	1/1	unmeasurable	16.492 (1.031-263.757)	0.0475
Tumor Regression Grade	Grade0-1b	Non-IC	42/72	65.3 (53.1-75.0)	1	
		IC	4/10	80.0 (40.9-94.6)	0.574 (0.205-1.604)	0.2894
	Grade2-3	Non-IC	20/45	73.3 (57.8-83.9)	1	
		IC	1/5	80.0 (20.4-96.9)	0.460 (0.062-3.430)	0.4489
Adjuvant chemotherapy	No	Non-IC	11/19	63.2 (37.9-80.4)	1	
		IC	0/1	100	unmeasurable	0.9942
	Yes	Non-IC	51/98	69.4 (59.2-77.5)	1	
		IC	5/14	78.6 (47.2-92.5)	0.644 (0.257-1.616)	0.3489