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Postoperative adjuvant chemotherapy in patients with gastric cancer based on the Nationwide Gastric Cancer Registry in Japan

Yasuhide Yamada[1,*], Yasuyuki Seto[2], Takaki Yoshikawa[3], Hiroya Takeuchi[4], Yuko Kitagawa[5], Yasuhiro Kodera[6], Yuichiro Doki[7], Kazuhiro Yoshida[8], Kei Muro[9], Yoshinori Kabeya[10], Ami Kamada[10], Kengo Nagashima[11], Hiraku Kumamaru[12], Hisateru Tachimori[13], Mitsuru Sasako[14], Hitoshi Katai[15], Hiroyuki Konno[16], Yoshihiro Kakeji[17,18]

[1] Department of Medical Research, National Center for Global Health and Medicine, Tokyo, Japan;
[2] National Cancer Center Hospital, Tokyo, Japan;
[3] Department of Gastric Surgery, National Cancer Center Hospital, Tokyo, Japan;
[4] Department of Surgery, Hamamatsu University, School of Medicine, Hamamatsu, Japan;
[5] Department of Surgery, Keio University, School of Medicine, Tokyo, Japan;
[6] NHO Nagoya Medical Center, Nagoya, Japan;
[7] Osaka University, Osaka, Japan;
[8] Gifu University, Gifu, Japan;
[9] Department of Pharmacotherapy, Aichi Cancer Center, Nagoya, Japan;
[10] Healthcare & Life Sciences, IBM Japan, Ltd, Tokyo, Japan;
[11] Biostatistics Unit, Clinical and Translational Research Center, Keio University Hospital, Tokyo, Japan;
[12] Department of Healthcare Quality Assessment, The University of Tokyo Graduate School of Medicine, Tokyo, Japan;
[13] Department of Health Policy and Management, Keio University School of Medicine, Tokyo, Japan;
[14] Yodogawa Christian Hospital, Osaka, Japan;
[15] Tachikawa Hospital, Tokyo, Japan;
[16] Hamamatsu University, School of Medicine, Hamamatsu, Japan;
[17] Database Committee, The Japanese Society of Gastroenterological Surgery, Tokyo, Japan;
[18] Division of Gastrointestinal Surgery, Department of Surgery, Kobe University Graduate School of Medicine, Kobe, Japan.

Abstract: The nationwide registry of the Japanese Gastric Cancer Association contains data related to the efficacy of adjuvant chemotherapy and prognostic factors across this patient population; elderly patients with advanced resectable gastric cancer are especially prevalent. Here, we analyzed data from 34,931 patients, who were treated between 2011 and 2013 at 421 hospitals in Japan. Although adjuvant chemotherapy was effective overall, 75 years or older elderly patients had a worse prognosis compared to younger patients. The most administered adjuvant chemotherapy was S-1 monotherapy. Adjuvant S-1 monotherapy was also effective for patients with pT1N2, pT1N3, and pT3N0 stage II tumors, as well as patients with other stage II and III malignancies. Independent prognostic factors for poor overall and relapse-free survival in patients at both stage II and stage III were age 75 or older, male, preoperative Eastern Cooperative Oncology Group performance status (ECOG-PS) 1 or more, preoperative renal dysfunction, undifferentiated adenocarcinoma, undergoing total gastrectomy, open laparotomy, no adjuvant chemotherapy, D1 lymphadenectomy, residual tumor R1 or R2, and Clavien-Dindo classification grade II or higher. Age 75 or older, renal dysfunction, ECOG-PS 1 and total gastrectomy were also significant risk factors for postoperative complications and lower compliance with adjuvant chemotherapy. Our analysis also revealed that adjuvant chemotherapy after resection of cancer of gastric remnant and postoperative chemotherapy against CY1 gastric cancer were also effective. We conclude that adjuvant chemotherapy is effective for all stage II and III patients including age 75 or older gastric cancer patients, in addition to distal gastrectomy, proximal gastrectomy, and pylorus-preserving surgery to avoid total gastrectomy may improve surgical outcomes and quality of life for elderly patients.

***Keywords*:** stomach cancer, lavage cytology, elderly patient, S-1, surgical site infection, postoperative complication, Clavien-Dindo

Introduction

Gastric cancer, a significant global health burden, remains the fifth most common malignancy worldwide, accounting for the fifth leading cause of cancer-related deaths (*1*). In 2022, the global incidence of gastric cancer reached 968,000 cases, with 660,000 individuals succumbing to the disease. Notably, Eastern Asian regions, including China, Japan, and Korea, exhibit disproportionately high incidence rates, with Mongolia recording the most cases per capita. Eastern Europe and South America also experience elevated rates, while Africa demonstrates the lowest incidence. Gastric cancer represents a leading cause of cancer mortality in some Central Asian countries. The etiological role of *Helicobacter pylori* infection in non-cardiac gastric cancer is well-established (*2*).

Gastrectomy with D2 lymphadenectomy has been the standard surgical approach for resectable gastric cancer in Japan. A paradigm shift has emerged, with a surgery-first approach followed by postoperative adjuvant chemotherapy using S-1 for stage II and a combination of S-1 and docetaxel or fluoropyrimidines and oxaliplatin for stage III gaining prominence (*3-14*). This shift was sustained by the findings of the JCOG0501 clinical trial, which demonstrated that preoperative chemotherapy with S-1 plus cisplatin did not confer a survival advantage for type 4 or large type 3 gastric cancer (*15*). The ACTS-GC trial, The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer, which compared postoperative S-1 monotherapy with surgery alone (*3,4*), included pStage II and III patients. It did not include patients with pT1N2, pT1N3, and pT3N0 tumors, because the Japanese Classification of Gastric Carcinoma, the 13th edition (*16*), did not include T1N2, T1N3, and T3N0 as Stage II in the Japanese Classification after the 14th edition (*17*). Therefore, the Gastric Cancer Treatment Guidelines 2021 of the Japanese Gastric Cancer Association (JGCA) (*18*) did not recommend adjuvant chemotherapy for such individuals yet. The surgical approach for advanced cancer of gastric remnant aligns with that of primary gastric cancer, which includes lymph node dissection (*19*). On the other hand, perioperative or postoperative chemotherapy has been the standard treatment paradigm for resectable advanced gastric cancer in China, Korea, and Western nations.

Regional variations in the efficacy of perioperative chemotherapy are attributable to differences in surgical techniques, medical infrastructure, and patient characteristics, such as obesity and comorbidities (*14,15,20-23*). Several factors have been identified as risk predictors for surgical site infection following gastrectomy, including male gender, age 60 or older, smoking, diabetes, anemia, preoperative obstruction, advanced TNM stage, hypoproteinemia, prolonged operative time, laparotomy, and blood transfusion (*24*). Postoperative infectious complications, which are more prevalent after D2 lymphadenectomy and in older patients, have been linked to poor adherence to adjuvant S-1 chemotherapy for gastric cancer (*25*).

To fully evaluate the efficacy of adjuvant chemotherapy in stage II and III primary gastric cancer, elderly patients, cancer of gastric remnant, and stage IV disease with positive lavage cytology without any other distant metastases, and identify prognostic factors across a diverse population, predictive factors of postoperative complication and compliance of postoperative adjuvant chemotherapy, we conducted a comprehensive analysis of data from the nationwide registry maintained by the JGCA.

Patients and Methods

Patients

Patients diagnosed with gastric cancer between January 1, 2011 and December 31, 2013 and registered with the JCGA nationwide registry of gastric cancer patients were enrolled in this study. Eligibility requirements were that patients had undergone surgery for gastric cancer at stage II and III, or that their cytology lavage result was positive according to the Japanese Classification of Gastric Carcinoma, the 14th edition (*17*), and UICC, Union for International Cancer Control, TNM classification, the 7th edition (*26*). The cases with cancer of gastric remnant were excluded from the analyses of primary gastric cancer. Patients who survived more than 8 weeks were analyzed in this study. Patients who received preoperative chemotherapy were excluded. This study was approved by the Ethics Review Committee of the National Center for Global Health and Medicine and opt-out informed consent was obtained.

Statistical analysis

Overall survival (OS) and relapse-free survival (RFS) were estimated using the Kaplan-Meier method, and confidence intervals (CI) were calculated based on the Greenwood formula. To address potential confounding factors in comparing the survival curves of two groups, 1:1 propensity score matching with the nearest neighbor method was implemented using logistic regression. The following binary variables were used to estimate propensity scores: age, sex, The American Society of Anesthesiologists classification of physical status (ASA-PS), Eastern Cooperative Oncology Group performance status (ECOG-PS), histology, operative approach, lymphadenectomy, residual tumor, methods of gastrectomy, and Clavien-Dindo (C-D) classification. To avoid issues with estimation, variables where the proportion of patients in one category was less than 10% were excluded from the covariates. The *glm* function from the *statsmodels* package was employed to conduct the propensity score matching process with a

caliper width of 0.1, ensuring closer matching between treatment and control units and improving covariate balance. Cases with missing data in any of the variables used for propensity score estimation were excluded from the analysis. To evaluate the quality of the matching, we compared the standardized mean differences of covariates between the two groups after matching. Our analysis confirmed that the standardized mean differences for all covariates were below 0.1, indicating a good balance. Hazard ratios (HR) for OS and RFS were obtained using Cox regression models. Possible prognostic factors were adjusted in multivariable analyses as appropriate. A two-sided p-value <0.05 was deemed significant. Moreover, propensity score matching was conducted to evaluate adjusted OS and PFS, where the propensity score was calculated by fitting the logistic regression model with the same prognostic factors as the Cox regression model. Logistic regression was used for determining the risk factors for postoperative complication and compliance with S-1 treatment in the adjuvant setting. Python version 3.9.7 with the *lifelines* package was used for all statistical analyses.

Results

Data from 34,931 patients with gastric cancer treated between 2011 and 2013 at 421 hospitals in Japan were collected. Among these, 15,848 patients had stage II and III disease, and 2,052 patients had stage IV disease that their cytology lavage result was positive (CY1) without any other distant metastases (Figure 1). Patient characteristics are described in Table 1 and Supplemental Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=96*). Pylorus-preserving gastrectomy was performed in only 0.5% of patients, proximal gastrectomy in 1.9%, and both segmental gastrectomy and local resection in 0.1% of overall patients each, while total gastrectomy was performed in 39.0% of all patients and in 37.5% of those who were 75 or older. Cisplatin combination chemotherapy comprised either S-1 or capecitabine. Other combination chemotherapies included capecitabine plus oxaliplatin, S-1 plus oxaliplatin, and S-1 plus docetaxel. The survival rates of elderly patients were at least 10 points lower than those of the total population (Figure 2).

Efficacy of postoperative chemotherapy in Stage II and III, the elderly, cancer of gastric remnant, and CY1

The efficacy of postoperative chemotherapy for stage II and III gastric cancer in terms of OS and RFS is shown in Figure 3 and Supplemental Figure S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=96*). Our analysis of this large dataset also revealed that adjuvant S-1 monotherapy for gastric cancer patients after surgical resection was effective in OS (Stage II, HR: 0.61, 95% CI: 0.54-0.69, $p < 0.001$; Stage III, HR: 0.54, 95% CI: 0.50-0.59, $p < 0.001$). Adjuvant S-1

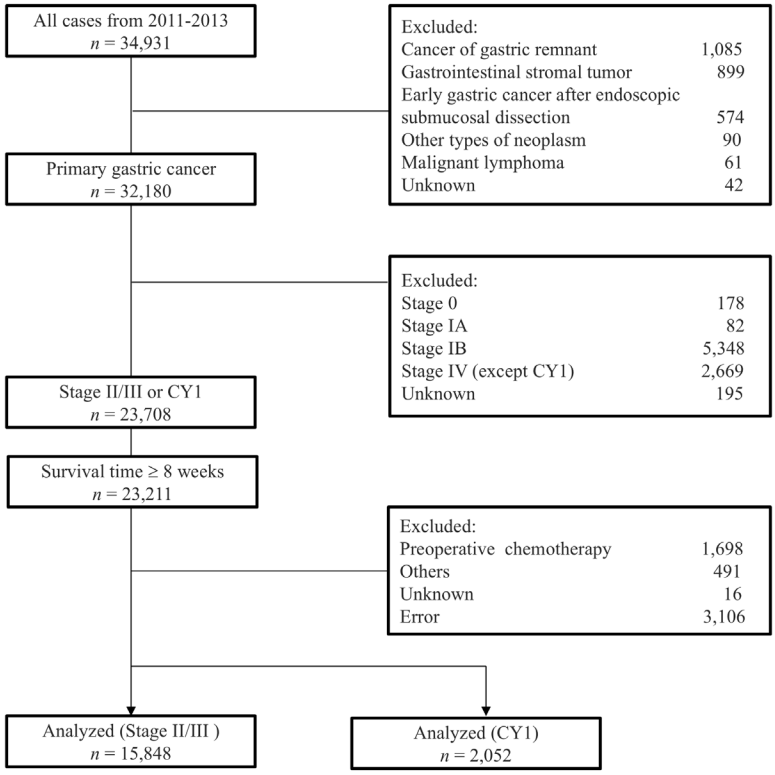


Figure 1. Flow diagram of the patient selection process. The cases with cancer of gastric remnant were excluded from the analyses of primary gastric cancer. Patients who survived more than 8 weeks were analyzed in this study. Patients who received preoperative chemotherapy were excluded. CY1, cancer cells on peritoneal cytology.

Table 1. Patient characteristics

Characteristics	Primary gastric cancer (*n* = 15,848)	75 or older, primary gastric cancer (*n* = 5,781)	Cancer of gastric remnant (*n* = 463)	CY1, gastric cancer (*n* = 2,052)
Age, median (range)	71.0 (38-88)	80.0 (75-88)	74.0 (40-88)	72.0 (38-88)
Sex				
Male	10,777 (68.0%)	3,828 (66.2%)	375 (81.0%)	1,366 (66.6%)
Female	5,071 (32.0%)	1,953 (33.8%)	88 (19.0%)	686 (33.4%)
ASA-PS				
1	3,385 (21.4%)	621 (10.7%)	69 (14.9%)	373 (18.2%)
2	9,497 (59.9%)	3,694 (63.9%)	317 (68.5%)	1,268 (61.8%)
≥ 3	1,957 (12.3%)	1,129 (19.5%)	51 (11.0%)	305 (14.9%)
ECOG-PS				
0	8,642 (54.5%)	2,491 (43.1%)	250 (54.0%)	943 (46.0%)
1	3,587 (22.6%)	1,694 (29.3%)	119 (25.7%)	551 (26.9%)
≥ 2	1,309 (8.3%)	791 (13.7%)	24 (5.2%)	238 (11.6%)
Creatinine clearance, median (mL/min)	67.3	51.5	60.8	62.4
Normal	7,180 (45.3%)	865 (15.0%)	160 (34.6%)	756 (36.8%)
Abnormal	7,779 (49.1%)	4,745 (82.1%)	284 (61.3%)	1,171 (57.1%)
Macroscopic morphology				
Type 0	2,242 (14.1%)	616 (10.7%)	60 (13.0%)	50 (2.4%)
Type 1	848 (5.4%)	401 (6.9%)	43 (9.3%)	40 (1.9%)
Type 2	5,028 (31.7%)	2,055 (35.5%)	114 (24.6%)	285 (13.9%)
Type 3	5,675 (35.8%)	1,990 (34.4%)	131 (28.3%)	876 (42.7%)
Type 4	1,244 (7.8%)	411 (7.1%)	59 (12.7%)	683 (33.3%)
Type 5	751 (4.7%)	283 (4.9%)	52 (11.2%)	111 (5.4%)
Location				
U, fundus	4,834 (30.5%)	1,755 (30.4%)	215 (46.4%)	839 (40.9%)
M, corpus	7,351 (46.4%)	2,449 (42.4%)	184 (39.7%)	1,145 (55.8%)
L, antrum and pylorus	7,462 (47.1%)	2,991 (51.7%)	42 (9.1%)	1,294 (63.1%)
T, total stomach	96 (0.6%)	45 (0.8%)	13 (2.8%)	54 (2.6%)
D, invasion to duodenum	499 (3.1%)	227 (3.9%)	7 (1.5%)	94 (4.6%)
E, invasion to esophagus	655 (4.1%)	255 (4.4%)	19 (4.1%)	111 (5.4%)
Histological type				
Differentiated adenocarcinoma				
pap	482 (3.0%)	208 (3.6%)	19 (4.1%)	34 (1.7%)
tub1	1,734 (10.9%)	699 (12.1%)	52 (11.2%)	142 (6.9%)
tub2	5,003 (31.6%)	2,065 (35.7%)	139 (30.0%)	481 (23.4%)
Undifferentiated adenocarcinoma				
por1	2,528 (16.0%)	1,046 (18.1%)	72 (15.6%)	243 (11.8%)
por2	4,442 (28.0%)	1,240 (21.4%)	123 (26.6%)	887 (43.2%)
sig	841 (5.3%)	189 (3.3%)	29 (6.3%)	134 (6.5%)
muc	484 (3.1%)	199 (3.4%)	17 (3.7%)	107 (5.2%)
Others	322 (2.0%)	128 (2.2%)	11 (2.4%)	21 (1.0%)
Gastrectomy				
Total gastrectomy	6,174 (39.0%)	2,168 (37.5%)	435 (94.0%)	1,134 (55.3%)
Distal gastrectomy	9,263 (58.4%)	3,440 (59.5%)	19 (4.1%)	901 (43.9%)
Pylorus-preserving gastrectomy	75 (0.5%)	15 (0.3%)	0 (0%)	3 (0.1%)
Proximal gastrectomy	300 (1.9%)	139 (2.4%)	0 (0%)	12 (0.6%)
Segmental gastrectomy	13 (0.1%)	7 (0.1%)	3 (0.6%)	2 (0.1%)
Local resection	23 (0.1%)	12 (0.2%)	6 (1.3%)	0 (0.0%)
Reconstruction				
B-I	4,493 (28.4%)	1,597 (27.6%)	4 (0.9%)	260 (12.7%)
B-II	718 (4.5%)	354 (6.1%)	7 (1.5%)	133 (6.5%)
DT	91 (0.6%)	29 (0.5%)	1 (0.2%)	10 (0.5%)
EG	185 (1.2%)	85 (1.5%)	0 (0%)	10 (0.5%)
IP	53 (0.3%)	29 (0.5%)	0 (0%)	2 (0.1%)
PP	67 (0.4%)	12 (0.2%)	0 (0%)	3 (0.1%)
RY	10,080 (63.6%)	3,603 (62.3%)	438 (94.6%)	1,619 (78.9%)
Others	74 (0.5%)	39 (0.7%)	6 (1.3%)	5 (0.2%)
NR	26 (0.2%)	9 (0.2%)	2 (0.4%)	0 (0.0%)

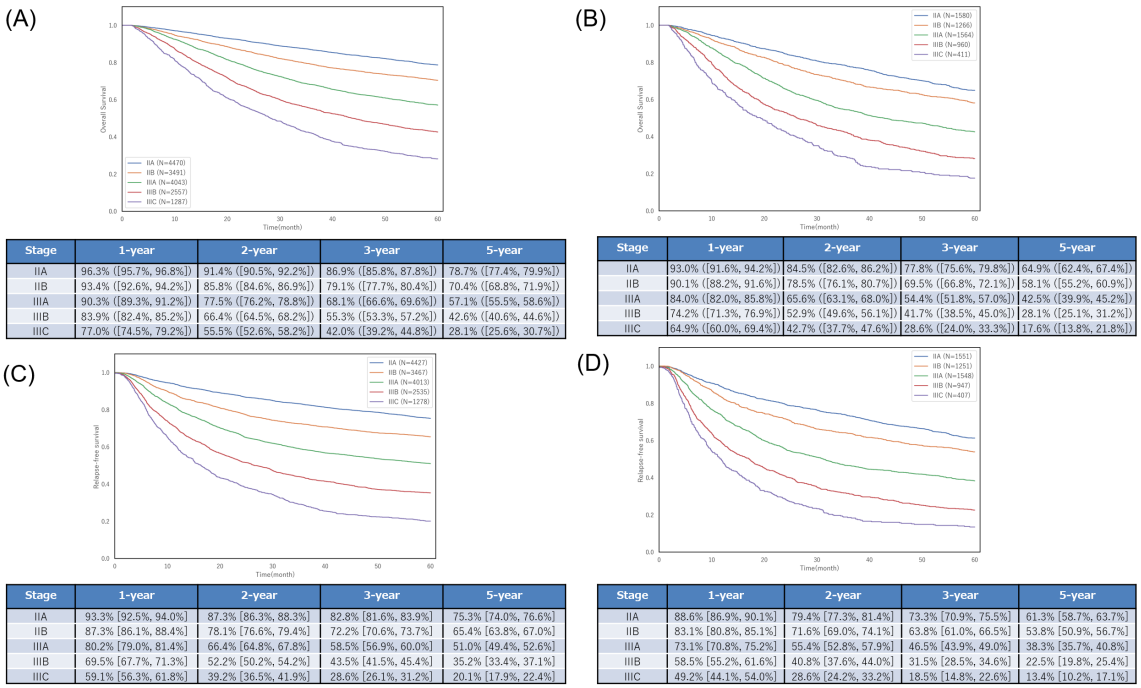
Abbreviations: ASA-PS, American Society of Anesthesiologists - physical status; B-I, Billroth I gastroduodenostomy; B-II, Billroth II gastrojejunostomy; Cap, capecitabine; CY1, cancer cells on peritoneal cytology; D0, no lymphadenectomy; D1, D1 lymphadenectomy; D2, D2 lymphadenectomy; DM, distal margin; DT, Double-tract method; ECOG-PS, Eastern Cooperative Oncology Group - performance status; EG, Esophagogastrostomy; IP, Jejunal interposition; muc, mucinous adenocarcinoma; NR, Non-resectional surgery; pap, papillary adenocarcinoma; PM, proximal margin; por1, solid type poorly differentiated adenocarcinoma; por2, non-solid type poorly differentiated adenocarcinoma; PP, Pylorus-preserving gastrectomy; R, residual tumor; RY, Roux-en-Y esophagojejunostomy or Roux-en-Y gastrojejunostomy; sig, signet-ring cell adenocarcinoma; tub1, well differentiated tubular adenocarcinoma; tub2, moderately differentiated adenocarcinoma.

Table 1. Patient characteristics (continued)

Characteristics	Primary gastric cancer (*n* = 15,848)	75 or older, primary gastric cancer (*n* = 5,781)	Cancer of gastric remnant (*n* = 463)	CY1, gastric cancer (*n* = 2,052)
Lymph node dissection				
D0	244 (1.5%)	128 (2.2%)	55 (11.9%)	217 (10.6%)
D1	1,197 (7.6%)	700 (12.1%)	100 (21.6%)	491 (23.9%)
D1+	3,223 (20.3%)	1,418 (24.5%)	91 (19.7%)	354 (17.3%)
D2	10,489 (66.2%)	3,323 (57.5%)	149 (32.2%)	889 (43.3%)
D2+	533 (3.4%)	143 (2.5%)	5 (1.1%)	70 (3.4%)
Approach				
Laparoscopic	2,828 (17.8%)	866 (15.0%)	23 (5.0%)	122 (5.9%)
Open	12,846 (81.1%)	4,850 (83.9%)	434 (93.7%)	1,914 (93.3%)
Others	174 (1.1%)	65 (1.1%)	6 (1.3%)	16 (0.8%)
pT-Depth of tumor invasion				
pT1a	72 (0.5%)	11 (0.2%)	2 (0.4%)	2 (0.1%)
pT1b	688 (4.3%)	232 (4.0%)	7 (1.5%)	13 (0.6%)
pT2	2,118 (13.4%)	725 (12.5%)	32 (6.9%)	17 (0.8%)
pT3	7,023 (44.3%)	2,554 (44.2%)	221 (47.7%)	173 (8.4%)
pT4a	5,448 (34.4%)	2,055 (35.5%)	131 (28.3%)	1,621 (79.0%)
pT4b	499 (3.1%)	204 (3.5%)	70 (15.1%)	223 (10.9%)
pN-Extent of lymph node metastasis				
pN0	3,920 (24.7%)	1,405 (24.3%)	232 (50.1%)	106 (5.2%)
pN1	3,850 (24.3%)	1,480 (25.6%)	106 (22.9%)	148 (7.2%)
pN2	4,050 (25.6%)	1,491 (25.8%)	79 (17.1%)	320 (15.6%)
pN3a	2,778 (17.5%)	1,018 (17.6%)	39 (8.4%)	625 (30.5%)
pN3b	1,250 (7.9%)	387 (6.7%)	7 (1.5%)	834 (40.6%)
pStage				
IIA	4,470 (28.2%)	1,580 (27.3%)	172 (37.1%)	-
IIB	3,491 (22.0%)	1,266 (21.9%)	118 (25.5%)	-
IIIA	4,043 (25.5%)	1,564 (27.1%)	97 (21.0%)	-
IIIB	2,557 (16.1%)	960 (16.6%)	58 (12.5%)	-
IIIC	1,287 (8.1%)	411 (7.1%)	18 (3.9%)	-
Proximal margin and distal margin				
PM0 and DM0	15,406 (97.2%)	5,564 (96.2%)	431 (93.1%)	1,758 (85.7%)
Others	368 (2.3%)	180 (3.1%)	27 (5.8%)	270 (13.2%)
Residual tumor				
R0	15,036 (94.9%)	5,406 (93.5%)	419 (90.5%)	326 (15.9%)
Others	763 (4.8%)	355 (6.1%)	44 (9.5%)	1,713 (83.5%)
Clavien-Dindo classification				
Grade I or none	13,089 (82.6%)	4,543 (78.6%)	345 (74.5%)	1,656 (80.7%)
Grade II	1,885 (11.9%)	820 (14.2%)	76 (16.4%)	249 (12.1%)
Grade III or higher	874 (5.5%)	418 (7.2%)	42 (9.1%)	147 (7.2%)
Postoperative chemotherapy	8,485 (53.5%)	1,645 (28.5%)	185 (40.0%)	974 (47.5%)
None	7,363 (46.5%)	4,136 (71.5%)	278 (60.0%)	1,078 (52.5%)
S-1 monotherapy	7,925 (50.0%)	1,597 (27.6%)	173 (37.4%)	616 (30.0%)
S-1 plus oxaliplatin	43 (0.3%)	9 (0.2%)	0 (0.0%)	3 (0.1%)
S-1 plus cisplatin	346 (2.2%)	20 (0.3%)	9 (1.9%)	295 (14.4%)
S-1 plus docetaxel	108 (0.7%)	15 (0.3%)	1 (0.2%)	50 (2.4%)
Cap plus oxaliplatin	59 (0.4%)	4 (0.1%)	2 (0.4%)	1 (0.0%)
Cap plus cisplatin	4 (0.0%)	0 (0.0%)	0 (0.0%)	9 (0.4%)

Abbreviations: ASA-PS, American Society of Anesthesiologists - physical status; B-I, Billroth I gastroduodenostomy; B-II, Billroth II gastrojejunostomy; Cap, capecitabine; CY1, cancer cells on peritoneal cytology; D0, no lymphadenectomy; D1, D1 lymphadenectomy; D2, D2 lymphadenectomy; DM, distal margin; DT, Double-tract method; ECOG-PS, Eastern Cooperative Oncology Group - performance status; EG, Esophagogastrostomy; IP, Jejunal interposition; muc, mucinous adenocarcinoma; NR, Non-resectional surgery; pap, papillary adenocarcinoma; PM, proximal margin; por1, solid type poorly differentiated adenocarcinoma; por2, non-solid type poorly differentiated adenocarcinoma; PP, Pylorus-preserving gastrectomy; R, residual tumor; RY, Roux-en-Y esophagojejunostomy or Roux-en-Y gastrojejunostomy; sig, signet-ring cell adenocarcinoma; tub1, well differentiated tubular adenocarcinoma; tub2, moderately differentiated adenocarcinoma.

monotherapy was also effective in patients with pT1N2, pT1N3, and pT3N0 stage II tumors, as well as in those with other stage II and III malignancies (Supplemental Figure S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=96*). The matched 5-year OS rates of pT1N2 and pT1N3 patients were 85.6% (95% CI: 79.6%-90.0%) in any adjuvant chemotherapy group and 73.7% (95% CI: 66.7%-79.5%) in surgery alone group (p = 0.004). The matched 5-year OS rates of pT3N0 patients were 88.1% (95% CI: 84.9%-90.6%) in any adjuvant chemotherapy group and 82.3% (95% CI: 78.7%-85.4%) in surgery alone group (p = 0.012). Compared to S-1 monotherapy, the efficacy of oxaliplatin combination therapy or S-1 plus docetaxel



(A)

Stage	1-year	2-year	3-year	5-year
IIA	96.3% ([95.7%, 96.8%])	91.4% ([90.5%, 92.2%])	86.9% ([85.8%, 87.8%])	78.7% ([77.4%, 79.9%])
IIB	93.4% ([92.6%, 94.2%])	85.8% ([84.6%, 86.9%])	79.1% ([77.7%, 80.4%])	70.4% ([68.8%, 71.9%])
IIIA	90.3% ([89.3%, 91.2%])	77.5% ([76.2%, 78.8%])	68.1% ([66.6%, 69.6%])	57.1% ([55.5%, 58.6%])
IIIB	83.9% ([82.4%, 85.2%])	66.4% ([64.5%, 68.2%])	55.3% ([53.3%, 57.2%])	42.6% ([40.6%, 44.6%])
IIIC	77.0% ([74.5%, 79.2%])	55.5% ([52.6%, 58.2%])	42.0% ([39.2%, 44.8%])	28.1% ([25.6%, 30.7%])

(B)

Stage	1-year	2-year	3-year	5-year
IIA	93.0% ([91.6%, 94.2%])	84.5% ([82.6%, 86.2%])	77.8% ([75.6%, 79.8%])	64.9% ([62.4%, 67.4%])
IIB	90.1% ([88.2%, 91.6%])	78.5% ([76.1%, 80.7%])	69.5% ([66.8%, 72.1%])	58.1% ([55.2%, 60.9%])
IIIA	84.0% ([82.0%, 85.8%])	65.6% ([63.1%, 68.0%])	54.4% ([51.8%, 57.0%])	42.5% ([39.9%, 45.2%])
IIIB	74.2% ([71.3%, 76.9%])	52.9% ([49.6%, 56.1%])	41.7% ([38.5%, 45.0%])	28.1% ([25.1%, 31.2%])
IIIC	64.9% ([60.0%, 69.4%])	42.7% ([37.7%, 47.6%])	28.6% ([24.0%, 33.3%])	17.6% ([13.8%, 21.8%])

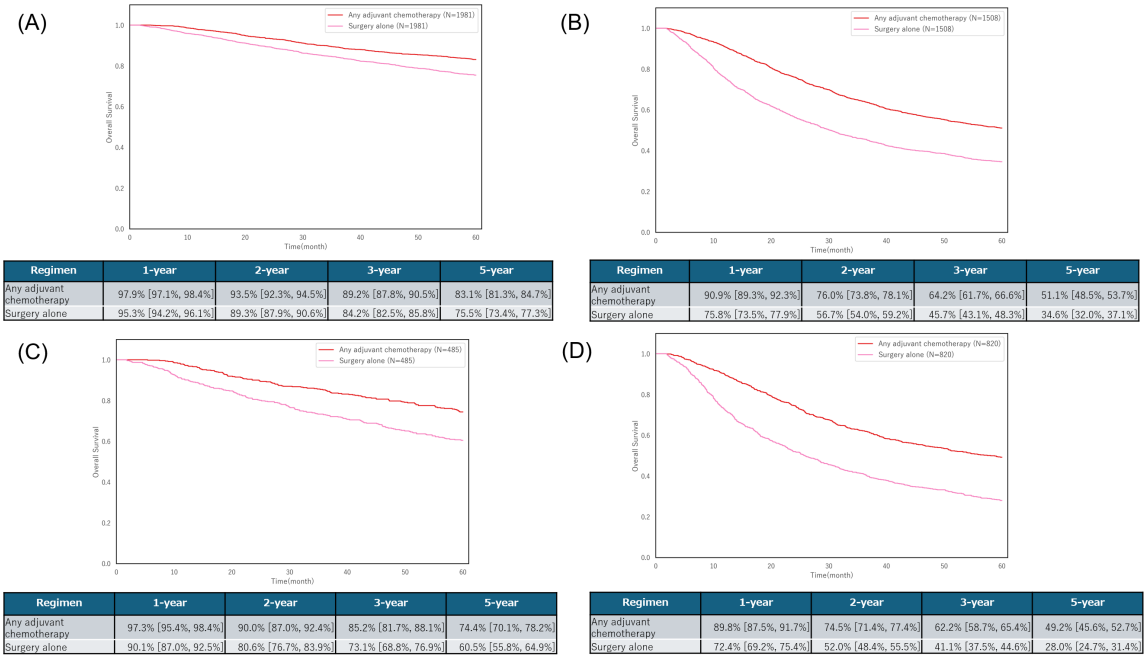
(C)

Stage	1-year	2-year	3-year	5-year
IIA	93.3% [92.5%, 94.0%]	87.3% [86.3%, 88.3%]	82.8% [81.6%, 83.9%]	75.3% [74.0%, 76.6%]
IIB	87.3% [86.1%, 88.4%]	78.1% [76.6%, 79.4%]	72.2% [70.6%, 73.7%]	65.4% [63.8%, 67.0%]
IIIA	80.2% [79.0%, 81.4%]	66.4% [64.8%, 67.8%]	58.5% [56.9%, 60.0%]	51.0% [49.4%, 52.6%]
IIIB	69.5% [67.7%, 71.3%]	52.2% [50.2%, 54.2%]	43.5% [41.5%, 45.4%]	35.2% [33.4%, 37.1%]
IIIC	59.1% [56.3%, 61.8%]	39.2% [36.5%, 41.9%]	28.6% [26.1%, 31.2%]	20.1% [17.9%, 22.4%]

(D)

Stage	1-year	2-year	3-year	5-year
IIA	88.6% [86.9%, 90.1%]	79.4% [77.3%, 81.4%]	73.3% [70.9%, 75.5%]	61.3% [58.7%, 63.7%]
IIB	83.1% [80.8%, 85.1%]	71.6% [69.0%, 74.1%]	63.8% [61.0%, 66.5%]	53.8% [50.9%, 56.7%]
IIIA	73.1% [70.8%, 75.2%]	55.4% [52.8%, 57.9%]	46.5% [43.9%, 49.0%]	38.3% [35.7%, 40.8%]
IIIB	58.5% [55.2%, 61.6%]	40.8% [37.6%, 44.0%]	31.5% [28.5%, 34.6%]	22.5% [19.8%, 25.4%]
IIIC	49.2% [44.1%, 54.0%]	28.6% [24.2%, 33.2%]	18.5% [14.8%, 22.6%]	13.4% [10.2%, 17.1%]

Figure 2. Overall and relapse-free survival of all stage II and III patients, and those age 75 or older. (A) Overall survival of all patients by stage, **(B)** Overall survival of age 75 or older patients by stage, **(C)** Relapse-free survival of all patients by stage, **(D)** Relapse-free survival of age 75 or older patients by stage.



(A)

Regimen	1-year	2-year	3-year	5-year
Any adjuvant chemotherapy	97.9% [97.1%, 98.4%]	93.5% [92.3%, 94.5%]	89.2% [87.8%, 90.5%]	83.1% [81.3%, 84.7%]
Surgery alone	95.3% [94.2%, 96.1%]	89.3% [87.9%, 90.6%]	84.2% [82.5%, 85.8%]	75.5% [73.4%, 77.3%]

(B)

Regimen	1-year	2-year	3-year	5-year
Any adjuvant chemotherapy	90.9% [89.3%, 92.3%]	76.0% [73.8%, 78.1%]	64.2% [61.7%, 66.6%]	51.1% [48.5%, 53.7%]
Surgery alone	75.8% [73.5%, 77.9%]	56.7% [54.0%, 59.2%]	45.7% [43.1%, 48.3%]	34.6% [32.0%, 37.1%]

(C)

Regimen	1-year	2-year	3-year	5-year
Any adjuvant chemotherapy	97.3% [95.4%, 98.4%]	90.0% [87.0%, 92.4%]	85.2% [81.7%, 88.1%]	74.4% [70.1%, 78.2%]
Surgery alone	90.1% [87.0%, 92.5%]	80.6% [76.7%, 83.9%]	73.1% [68.8%, 76.9%]	60.5% [55.8%, 64.9%]

(D)

Regimen	1-year	2-year	3-year	5-year
Any adjuvant chemotherapy	89.8% [87.5%, 91.7%]	74.5% [71.4%, 77.4%]	62.2% [58.7%, 65.4%]	49.2% [45.6%, 52.7%]
Surgery alone	72.4% [69.2%, 75.4%]	52.0% [48.4%, 55.5%]	41.1% [37.5%, 44.6%]	28.0% [24.7%, 31.4%]

Figure 3. Matched analysis of overall survival for all patients and those age 75 or older patients with or without adjuvant chemotherapy at stage II and III. (A) Overall survival of matched patients at stage II, **(B)** Overall survival of matched patients at stage III, **(C)** Overall survival of matched age 75 or older patients at stage II, **(D)** Overall survival of matched age 75 or older patients by stage III. Age, sex, American Society of Anesthesiologists classification of physical status, Eastern Cooperative Oncology Group performance status, histology, operative approach, lymphadenectomy, residual tumor, methods of gastrectomy, and Clavien-Dindo classification were adjusted for propensity score matching.

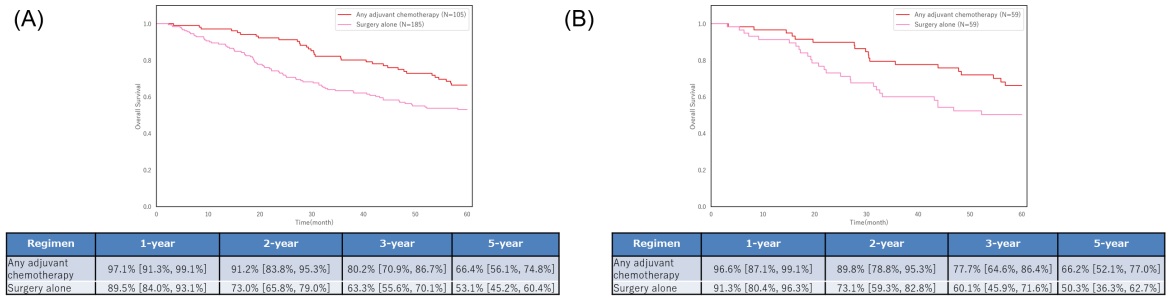
therapy was similar for stage II (HR: 0.75, 95% CI: 0.24-0.36, $p = 0.629$) and superior for stage III (HR: 0.66, 95% CI: 0.48-0.89, $p = 0.007$) (Supplemental Figure S3 and S4, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=96*) The OS of patients treated with cisplatin was inferior to those who received S-1 monotherapy (Stage II, HR: 2.00, 95% CI: 1.01-3.94, $p = 0.047$; Stage III, HR: 1.31, 95% CI: 1.09-1.57, $p = 0.004$). Across the whole population, some form of adjuvant chemotherapy was given to 45.2% and 63.0%

of stage II and stage III patients, respectively; for patients over age 75 years these figures were 20.9% and 35.8%. The most administered adjuvant chemotherapy was S-1 monotherapy. Adjuvant chemotherapy after resection of cancer of gastric remnant (Figure 4; Supplemental Figure S5, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=96*) and post-operative chemotherapy against CY1 gastric cancer were also effective (Figure 5).

Prognostic factors of stage II and III gastric cancer

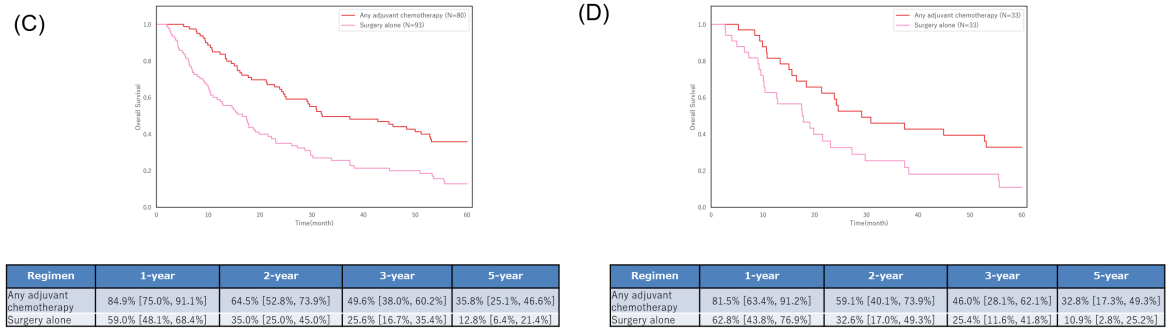
Independent prognostic factors for poor OS and RFS in patients with both stage II and stage III disease were: age 75 or older, male, preoperative ECOG-PS ≥ 1, preoperative renal dysfunction, total gastrectomy, D1 lymphadenectomy, open laparotomy, residual tumor R1 or R2, and C-D classification grade II or higher, no adjuvant chemotherapy (Table 2 and Table 3). Preoperative ASA-PS was not a statistically significant prognostic factor for OS and RFS at stage III but stage II. Undifferentiated carcinoma, which consisted of solid and non-solid types of poorly differentiated adenocarcinoma and signet ring cell carcinoma, was an independent prognostic factor for OS in both stage II and III disease. In the total population, the incidence rates of C-D grade II or more in patients with stage II and III disease were 10.5% (183/1,735) in those who underwent D1 lymphadenectomy and 13.2% (874/6,630) in those who underwent D2 lymphadenectomy. The HR for OS in D2 versus D1 lymphadenectomy was 0.78 ($p < 0.001$) for stage II patients and 0.81 ($p < 0.001$) for stage III patients (Table 2). In patients age 75 or older, these rates were 14.7% (46/436) for D1 and 14.8% for D2 lymphadenectomy. For laparoscopic surgery versus open surgery, multivariate analyses yielded a HR of 0.83 (95% CI: 0.72-0.95, $p = 0.006$) for stage II patients and 0.85 (95% CI: 0.75-0.96, $p = 0.007$) for stage III patients. Thus, laparoscopic surgery is an independent favorable prognostic factor for OS.

The OS of patients with postoperative complications classified as C-D grade II or higher was shorter than that of patients without complications or with C-D grade I (Figure 6; Supplemental Figure S6, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=96*). Logistic regression showed that age 75 or older, male, renal dysfunction, ECOG-PS or more 1, and total gastrectomy were all correlated significantly with a higher incidence of C-D grade II or more disease ($p < 0.01$) (Table 4). In age 75 or older patients, male, ECOG-PS 1 or more, total gastrectomy were correlated significantly with a higher incidence of C-D grade II or more disease. Age 75 or older, renal dysfunction, ECOG-PS 1 or more, total gastrectomy, stage III disease, and C-D grade II or higher all correlated with a lower compliance with adjuvant S-1 chemotherapy ($p < 0.01$).



Regimen	1-year	2-year	3-year	5-year
Any adjuvant chemotherapy	97.1% [91.3%, 99.1%]	91.2% [83.8%, 95.3%]	80.2% [70.9%, 86.7%]	66.4% [56.1%, 74.8%]
Surgery alone	89.5% [84.0%, 93.1%]	73.0% [65.8%, 79.0%]	63.3% [55.6%, 70.1%]	53.1% [45.2%, 60.4%]

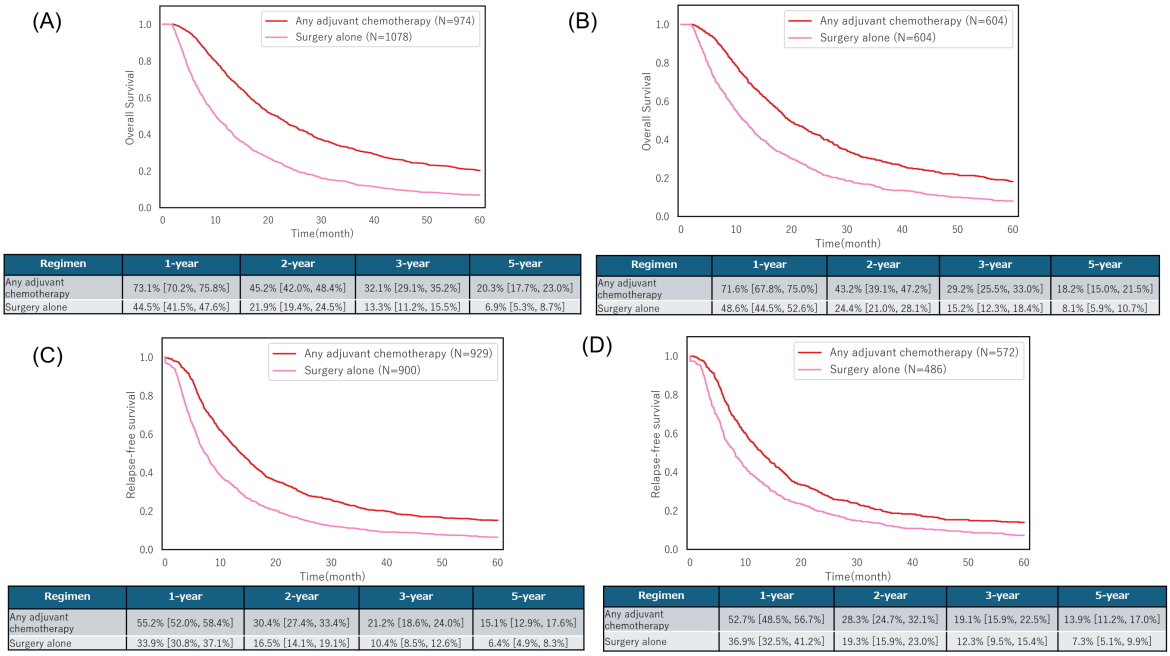
Regimen	1-year	2-year	3-year	5-year
Any adjuvant chemotherapy	96.6% [87.1%, 99.1%]	89.8% [78.8%, 95.3%]	77.7% [64.6%, 86.4%]	66.2% [52.1%, 77.0%]
Surgery alone	91.3% [80.4%, 96.3%]	73.1% [59.3%, 82.8%]	60.1% [45.9%, 71.6%]	50.3% [36.3%, 62.7%]



Regimen	1-year	2-year	3-year	5-year
Any adjuvant chemotherapy	84.9% [75.0%, 91.1%]	64.5% [52.8%, 73.9%]	49.6% [38.0%, 60.2%]	35.8% [25.1%, 46.6%]
Surgery alone	59.0% [48.1%, 68.4%]	35.0% [25.0%, 45.0%]	25.6% [16.7%, 35.4%]	12.8% [6.4%, 21.4%]

Regimen	1-year	2-year	3-year	5-year
Any adjuvant chemotherapy	81.5% [63.4%, 91.2%]	59.1% [40.1%, 73.9%]	46.0% [28.1%, 62.1%]	32.8% [17.3%, 49.3%]
Surgery alone	62.8% [43.8%, 76.9%]	32.6% [17.0%, 49.3%]	25.4% [11.6%, 41.8%]	10.9% [2.8%, 25.2%]

Figure 4. Overall survival of pre-matched and matched patients with cancer of gastric remnant with or without adjuvant chemotherapy. (A) Overall survival of pre-matched patients who have equivalent depth of tumor invasion and extent of lymph node metastasis to stage II, **(B)** Overall survival of matched patients equivalent to stage II, **(C)** Overall survival of pre-matched patients equivalent to stage II, **(D)** Overall survival of matched patients equivalent to stage III. Age, sex, American Society of Anesthesiologists classification of physical status, Eastern Cooperative Oncology Group performance status, histology, operative approach, lymphadenectomy, residual tumor, methods of gastrectomy, and Clavien-Dindo classification were adjusted for propensity score matching.



Regimen	1-year	2-year	3-year	5-year
Any adjuvant chemotherapy	73.1% [70.2%, 75.8%]	45.2% [42.0%, 48.4%]	32.1% [29.1%, 35.2%]	20.3% [17.7%, 23.0%]
Surgery alone	44.5% [41.5%, 47.6%]	21.9% [19.4%, 24.5%]	13.3% [11.2%, 15.5%]	6.9% [5.3%, 8.7%]

Regimen	1-year	2-year	3-year	5-year
Any adjuvant chemotherapy	71.6% [67.8%, 75.0%]	43.2% [39.1%, 47.2%]	29.2% [25.5%, 33.0%]	18.2% [15.0%, 21.5%]
Surgery alone	48.6% [44.5%, 52.6%]	24.4% [21.0%, 28.1%]	15.2% [12.3%, 18.4%]	8.1% [5.9%, 10.7%]

Regimen	1-year	2-year	3-year	5-year
Any adjuvant chemotherapy	55.2% [52.0%, 58.4%]	30.4% [27.4%, 33.4%]	21.2% [18.6%, 24.0%]	15.1% [12.9%, 17.6%]
Surgery alone	33.9% [30.8%, 37.1%]	16.5% [14.1%, 19.1%]	10.4% [8.5%, 12.6%]	6.4% [4.9%, 8.3%]

Regimen	1-year	2-year	3-year	5-year
Any adjuvant chemotherapy	52.7% [48.5%, 56.7%]	28.3% [24.7%, 32.1%]	19.1% [15.9%, 22.5%]	13.9% [11.2%, 17.0%]
Surgery alone	36.9% [32.5%, 41.2%]	19.3% [15.9%, 23.0%]	12.3% [9.5%, 15.4%]	7.3% [5.1%, 9.9%]

Figure 5. Postoperative systemic chemotherapy in pre-matched and matched CY1 gastric cancer patients. (A) Overall survival of pre-matched CY1 gastric cancer patients, **(B)** Overall survival of matched CY1 gastric cancer patients, **(C)** Relapse-free survival of pre-matched CY1 patients, **(D)** Relapse-free survival of matched CY1 patients. Age, sex, American Society of Anesthesiologists classification of physical status, Eastern Cooperative Oncology Group performance status, histology, operative approach, lymphadenectomy, residual tumor, methods of gastrectomy, and Clavien-Dindo classification were adjusted for propensity score matching.

Discussion

Our real-world analysis of the large JGCA dataset reveals that postoperative chemotherapy is effective for age 75 or older patients as well as less than 75 with advanced stage II and III resectable primary gastric cancer without C-D II or more complications, cancer of gastric remnant, and stage IV disease with CY1 without any other distant metastases.

Because we found that adjuvant chemotherapy was effective in patients with pT1N2, pT1N3, and pT3N0 in the current retrospective study, we suggest that adjuvant chemotherapy should be also recommended for these individuals although it is difficult to conduct clinical trials to compare adjuvant chemotherapy with surgery alone for these limited cases with pT1N2, pT1N3, and pT3N0 with the similar risk of recurrence for the other stage II. Until the 13th edition of the Japanese Classification of Gastric Carcinoma, lymph nodes were classified based on the anatomical location of the primary tumor within the stomach. This anatomical classification was used to determine the extent of lymph node metastasis, N1-N3, M1 and staging, as well as to define the extent of lymph node dissection, D1-D3. Although this method was rational, based on extensive data accumulation and detailed analysis over many years, it was complex and difficult for general surgeons and overseas specialists to fully understand. Additionally, the determination of the primary tumor location and metastatic lymph node sites sometimes lacked objectivity. In the 14th edition of the Japanese Classification of Gastric Carcinoma, this anatomical N classification was abolished, and an N classification based on the number of metastatic lymph nodes, linked to the TNM classification, was adopted. This change was made because studies both domestically and internationally have shown that classification based on the number of metastatic lymph nodes better reflects prognosis than anatomical classification, and to emphasize international universality and objectivity (*18*).

Age 75 or older, male, preoperative ECOG-PS 1 or more, preoperative renal dysfunction, total gastrectomy, D1 lymph node dissection, open laparotomy, residual tumor R1 or R2, undifferentiated carcinoma, and C-D classification grade II or higher, and no adjuvant chemotherapy were the independent prognostic factors for poor OS in patients with both stage II and stage III disease. The predictive factors of C-D II or higher which is one of the worse prognostic factors were 75 or older age, male, preoperative renal dysfunction, preoperative ECOG-PS 1 or more, total gastrectomy, except lymphadenectomy. A few of earlier randomized controlled trials where the risk of recurrence after curative resection was not significantly different for patients who underwent D1 or D2 lymphadenectomy due to high mortality of D2, lack of quality control of surgical skills, or inadequate lymph node dissection in obese patients (*23,27*). Additionally, patients who underwent D2 lymphadenectomy reportedly have significantly higher postoperative morbidity compared with those who underwent a D1 procedure (*23,28-32*). Hemorrhage,

Table 2. Prognostic factors of overall survival in patients with primary gastric cancer at stage II and III by univariate and multivariate analyses

Factors		Univariate analysis					Multivariate analysis			
Covariate	*n*	HR	95% CI (lower)	95% CI (upper)	*p*-value	*n*	HR	95% CI (lower)	95% CI (upper)	*p*-value
Stage II										
Age (≥ 75 *vs.* < 75)	7,738	2.57	2.34	2.82	< 0.001	6,223	1.69	1.49	1.93	< 0.001
Sex (male *vs.* female)	7,961	1.39	1.26	1.54	< 0.001	6,223	1.44	1.28	1.63	< 0.001
Preoperative_ASA-PS (1 *vs.* 2 or more)	7,423	0.43	0.38	0.50	< 0.001	6,223	0.68	0.58	0.80	< 0.001
Preoperative_ECOG-PS (0 *vs.*1or more)	6,770	0.57	0.51	0.63	< 0.001	6,223	0.77	0.69	0.86	< 0.001
Preoperative_CCr (more than the upper limit *vs.* normal)	7,533	2.30	2.08	2.54	< 0.001	6,223	1.31	1.16	1.49	< 0.001
Macroscopic morphology (type 4 *vs.* others)	7,927	1.93	1.60	2.32	< 0.001					
Location (UML *vs.* others)	7,961	2.72	1.41	5.23	0.003					
Histology (differentiated *vs.* undifferentiated)	7,773	1.15	1.05	1.26	0.003	6,223	0.89	0.80	0.99	0.026
Method of resection (total gastrectomy *vs.* others)	7,961	1.29	1.18	1.42	< 0.001	6,223	1.29	1.16	1.44	< 0.001
Lymphadenectomy (D2 *vs.* D1)	7,887	0.63	0.58	0.69	< 0.001	6,223	0.78	0.70	0.87	< 0.001
Approach (laparoscope *vs.* others)	7,961	0.75	0.67	0.84	< 0.001	6,223	0.83	0.72	0.95	0.006
Depth of tumor invasion (pT4 *vs.* pT1-T3)	7,961	1.48	1.31	1.67	< 0.001					
Extent of lymph node metastasis (pN0/N1 *vs.* pN2/N3)	7,961	1.11	0.98	1.26	0.087					
Proximal margin and distal margin (PM0 and DM0 *vs.* others)	7,928	0.32	0.24	0.43	< 0.001					
Residual tumor (R0 *vs.* others)	7,930	0.35	0.27	0.45	< 0.001	6,223	0.35	0.27	0.47	< 0.001
Clavien-Dindo classification (Grade II or more *vs.* others)	7,961	1.64	1.47	1.83	< 0.001	6,223	1.29	1.13	1.46	< 0.001
Adjuvant chemotherapy (any chemotherapy except cisplatin *vs.* surgery alone)	7,928	0.42	0.38	0.47	< 0.001	6,223	0.63	0.56	0.71	< 0.001
Stage III										
Age (≥ 75 *vs.* < 75)	7,643	1.96	1.84	2.10	< 0.001	5,981	1.34	1.22	1.46	< 0.001
Sex (male *vs.* female)	7,887	1.20	1.12	1.29	< 0.001	5,981	1.26	1.16	1.37	< 0.001
Preoperative_ASA-PS (1 *vs.*2 or more)	7,416	0.68	0.63	0.74	< 0.001	5,981	0.92	0.83	1.02	0.098
Preoperative_ECOG-PS (0 *vs.*1or more)	6,768	0.65	0.61	0.70	< 0.001	5,981	0.82	0.76	0.89	< 0.001
Preoperative_CCr (more than the upper limit *vs.* normal)	7,426	1.69	1.58	1.80	< 0.001	5,981	1.14	1.05	1.25	0.002
Macroscopic morphology (type 4 *vs.* others)	7,861	1.78	1.64	1.94	< 0.001					
Location (UML *vs.* Other)	7,887	1.68	1.27	2.23	< 0.001					
Histology (differentiated *vs.* undifferentiated)	7,741	0.88	0.82	0.94	< 0.001	5,981	0.78	0.72	0.84	< 0.001
Method of resection (total gastrectomy *vs.* others)	7,887	1.28	1.20	1.37	< 0.001	5,981	1.27	1.18	1.37	< 0.001
Lymphadenectomy (D2 *vs.* D1)	7,799	0.60	0.56	0.64	< 0.001	5,981	0.81	0.74	0.88	< 0.001
Approach (laparoscope *vs.* others)	7,887	0.77	0.69	0.85	< 0.001	5,981	0.85	0.75	0.96	0.007
Depth of tumor invasion (pT4 *vs.* pT1-T3)	7,887	1.49	1.40	1.60	< 0.001					
Extent of lymph node metastasis (pN1 *vs.* pN2/N3)	7,887	0.74	0.67	0.81	< 0.001					
Proximal margin and distal margin (PM0 and DM0 *vs.* others)	7,846	0.40	0.35	0.46	< 0.001					
Residual tumor (R0 *vs.* others)	7,798	0.40	0.37	0.45	< 0.001	5,981	0.48	0.42	0.54	< 0.001
Clavien-Dindo classification (Grade II or more *vs.* others)	7,887	1.47	1.36	1.59	< 0.001	5,981	1.21	1.11	1.33	< 0.001
Adjuvant chemotherapy (any chemotherapy except cisplatin *vs.* surgery alone)	7,570	0.40	0.37	0.42	< 0.001	5,981	0.53	0.49	0.58	< 0.001

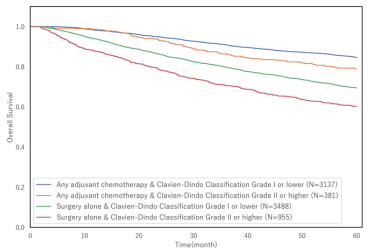
Abbreviations: 95% CI, 95% confidence interval; ASA-PS, American Society of Anesthesiologists - physical status; CCr, creatinine clearance; D1, D1 lymphadenectomy; D2, D2 lymphadenectomy; differentiated, differentiated carcinoma which consists of papillary adenocarcinoma, well differentiated tubular adenocarcinoma, and moderately differentiated adenocarcinoma; DM, distal margin, ECOG-PS, Eastern Cooperative Oncology Group - performance status; HR, hazard ratio; PM, proximal margin; R, residual tumor; UML, Fundus, Corpus, and Antrum and pylorus; undifferentiated, undifferentiated carcinoma which consists of solid type poorly differentiated adenocarcinoma, non-solid type poorly differentiated adenocarcinoma, signet-ring cell adenocarcinoma, and mucinous adenocarcinoma.

Table 3. Prognostic factors of relapse-free survival in patients with primary gastric cancer at stage II and III by univariate and multivariate analyses

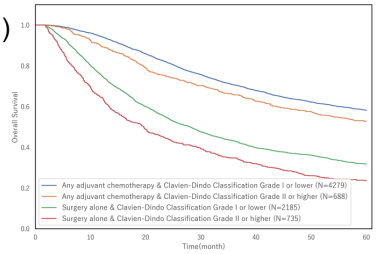
Factors	Univariate analysis					Multivariate analysis				
Covariate	*n*	HR	95% CI (lower)	95% CI (upper)	*p*-value	*n*	HR	95% CI (lower)	95% CI (upper)	*p*-value
Stage II										
Age (≥ 75 *vs*. <75)	7,674	2.26	2.07	2.46	< 0.001	6,171	1.65	1.47	1.86	< 0.001
Sex (male *vs*. female)	7,894	1.36	1.24	1.50	< 0.001	6,171	1.39	1.24	1.55	< 0.001
Preoperative_ASA-PS (1 *vs*. 2 or more)	7,361	0.49	0.44	0.56	< 0.001	6,171	0.73	0.64	0.85	< 0.001
Preoperative_ECOG-PS (0 *vs*. 1 or more)	6,715	0.60	0.55	0.65	< 0.001	6,171	0.77	0.70	0.85	< 0.001
Preoperative_CCr (more than the upper limit *vs*. normal)	7,475	1.97	1.80	2.15	< 0.001	6,171	1.17	1.04	1.32	0.007
Macroscopic morphology (type 4 *vs*. others)	7,860	1.95	1.65	2.31	< 0.001					
Location (UML *vs*. others)	7,894	2.79	1.55	5.05	< 0.001					
Histology (differentiated *vs*. undifferentiated)	7,707	1.20	1.10	1.30	< 0.001	6,171	0.96	0.87	1.05	0.361
Method of resection (total gastrectomy *vs*. others)	7,894	1.31	1.20	1.42	< 0.001	6,171	1.28	1.16	1.41	< 0.001
Lymphadenectomy (D2 *vs*. D1)	7,820	0.68	0.62	0.74	< 0.001	6,171	0.81	0.73	0.90	< 0.001
Approach (laparoscope *vs*. others)	7,894	0.74	0.67	0.83	< 0.001	6,171	0.82	0.72	0.92	0.001
Depth of tumor invasion (pT4 *vs*. pT1-T3)	7,894	1.50	1.34	1.67	< 0.001					
Extent of lymph node metastasis (pN0/N1 *vs*. pN2/N3)	7,894	1.08	0.97	1.21	0.181					
Proximal margin and distal margin (PM0 and DM0 *vs*. others)	7,862	0.33	0.25	0.44	< 0.001					
Residual tumor (R0 *vs*. others)	7,863	0.35	0.27	0.44	< 0.001	6,171	0.34	0.26	0.44	< 0.001
Clavien-Dindo classification (Grade II or more *vs*. others)	7,894	1.54	1.39	1.70	< 0.001	6,171	1.24	1.10	1.40	< 0.001
Adjuvant chemotherapy (any chemotherapy except cisplatin *vs*. surgery alone)	7,861	0.51	0.47	0.56	< 0.001	6,171	0.72	0.65	0.81	< 0.001
Stage III										
Age (≥ 75 *vs*. <75)	7,586	1.70	1.60	1.81	< 0.001	5,939	1.22	1.12	1.33	< 0.001
Sex (male *vs*. female)	7,826	1.19	1.11	1.27	< 0.001	5,939	1.20	1.12	1.30	< 0.001
Preoperative_ASA-PS (1 *vs*. 2 or more)	7,361	0.72	0.67	0.78	< 0.001	5,939	0.92	0.84	1.01	0.077
Preoperative_ECOG-PS (0 *vs*. 1 or more)	6,721	0.70	0.65	0.74	< 0.001	5,939	0.86	0.80	0.92	< 0.001
Preoperative_CCr (more than the upper limit *vs*. normal)	7,372	1.54	1.45	1.64	< 0.001	5,939	1.16	1.07	1.25	< 0.001
Macroscopic morphology (type 4 *vs*. others)	7,801	1.72	1.59	1.87	< 0.001					
Location (UML *vs*. Other)	7,826	1.64	1.26	2.14	< 0.001					
Histology (differentiated *vs*. undifferentiated)	7,680	0.95	0.89	1.01	0.084	5,939	0.86	0.80	0.93	< 0.001
Method of resection (total gastrectomy *vs*. others)	7,826	1.26	1.19	1.33	< 0.001	5,939	1.24	1.16	1.33	< 0.001
Lymphadenectomy (D2 *vs*. D1)	7,739	0.65	0.61	0.69	< 0.001	5,939	0.85	0.78	0.92	< 0.001
Approach (laparoscope *vs*. others)	7,826	0.79	0.72	0.87	< 0.001	5,939	0.86	0.77	0.96	0.006
Depth of tumor invasion (pT4 *vs*. T1-T3)	7,826	1.43	1.34	1.52	< 0.001					
Extent of lymph node metastasis (pN0/N1 *vs*. N2/N3)	7,826	0.71	0.65	0.77	< 0.001					
Proximal margin and distal margin (PM0 and DM0 *vs*. others)	7,785	0.43	0.37	0.49	< 0.001					
Residual tumor (R0 *vs*. others)	7,738	0.43	0.39	0.48	< 0.001	5,939	0.50	0.45	0.56	< 0.001
Clavien-Dindo classification (Grade II or more *vs*. others)	7,826	1.40	1.31	1.51	< 0.001	5,939	1.20	1.10	1.30	< 0.001
Adjuvant chemotherapy (any chemotherapy except cisplatin *vs*. surgery alone)	7,511	0.47	0.44	0.5	< 0.001	5,939	0.61	0.56	0.66	< 0.001

Abbreviations: 95% CI, 95% confidence interval; ASA-PS, American Society of Anesthesiologists- physical status; CCr, creatinine clearance; D1, D1 lymphadenectomy; D2, D2 lymphadenectomy; differentiated, differentiated carcinoma which consists of papillary adenocarcinoma, well differentiated tubular adenocarcinoma, and moderately differentiated adenocarcinoma; DM, distal margin, ECOG-PS, Eastern Cooperative Oncology Group-performance status; HR, hazard ratio; PM, proximal margin; R, residual tumor; UML, Fundus, Corpus, and Antrum and pylorus; undifferentiated, undifferentiated carcinoma which consists of solid type poorly differentiated adenocarcinoma, non-solid type poorly differentiated adenocarcinoma, signet-ring cell adenocarcinoma, and mucinous adenocarcinoma.

(A)

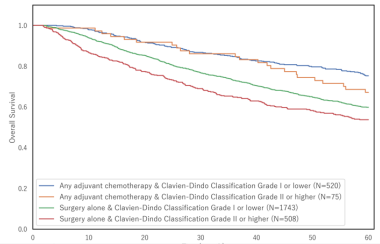


(B)

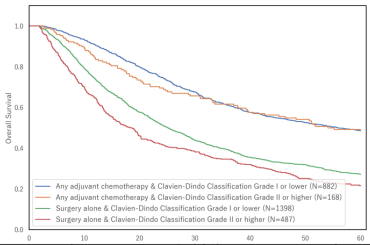


Subpopulation	Regimen & Clavien-Dindo Classification Grade	1-year	2-year	3-year	5-year
Stage II	Any adjuvant chemotherapy & Clavien-Dindo Classification Grade I or lower	98.1% [97.6%, 98.6%]	94.7% [93.9%, 95.4%]	90.9% [89.9%, 91.9%]	84.7% [83.3%, 85.9%]
	Any adjuvant chemotherapy & Clavien-Dindo Classification Grade II or higher	98.7% [96.8%, 99.4%]	93.0% [89.8%, 95.2%]	86.3% [82.4%, 89.5%]	79.0% [74.4%, 82.9%]
	Surgery alone & Clavien-Dindo Classification Grade I or lower	93.8% [93.0%, 94.6%]	86.0% [84.8%, 87.2%]	79.7% [78.3%, 81.1%]	69.5% [67.8%, 71.0%]
	Surgery alone & Clavien-Dindo Classification Grade II or higher	87.7% [85.4%, 89.7%]	78.3% [75.5%, 80.8%]	70.5% [67.4%, 73.4%]	60.3% [56.9%, 63.5%]
Stage III	Any adjuvant chemotherapy & Clavien-Dindo Classification Grade I or lower	94.3% [93.5%, 94.9%]	81.5% [80.3%, 82.7%]	70.6% [69.2%, 72.0%]	58.2% [56.7%, 59.7%]
	Any adjuvant chemotherapy & Clavien-Dindo Classification Grade II or higher	89.6% [87.0%, 91.7%]	74.7% [71.2%, 77.8%]	65.9% [62.1%, 69.3%]	52.7% [48.8%, 56.5%]
	Surgery alone & Clavien-Dindo Classification Grade I or lower	75.3% [73.4%, 77.1%]	54.4% [52.2%, 56.5%]	43.1% [40.9%, 45.3%]	31.7% [29.6%, 33.9%]
	Surgery alone & Clavien-Dindo Classification Grade II or higher	64.5% [60.8%, 67.9%]	44.2% [40.4%, 47.9%]	34.7% [31.1%, 38.4%]	23.6% [20.4%, 27.0%]

(C)



(D)



Subpopulation	Regimen & Clavien-Dindo Classification Grade	1-year	2-year	3-year	5-year
Stage II	Any adjuvant chemotherapy & Clavien-Dindo Classification Grade I or lower	96.5% [94.5%, 97.8%]	89.5% [86.5%, 91.9%]	84.7% [81.2%, 87.5%]	75.3% [71.2%, 78.9%]
	Any adjuvant chemotherapy & Clavien-Dindo Classification Grade II or higher	97.3% [89.6%, 99.3%]	91.7% [82.5%, 96.2%]	86.1% [75.7%, 92.3%]	67.1% [54.8%, 76.8%]
	Surgery alone & Clavien-Dindo Classification Grade I or lower	92.0% [90.6%, 93.2%]	81.3% [79.4%, 83.1%]	73.0% [70.8%, 75.1%]	59.8% [57.3%, 62.2%]
	Surgery alone & Clavien-Dindo Classification Grade II or higher	84.5% [81.0%, 87.4%]	73.9% [69.7%, 77.6%]	64.8% [60.3%, 69.0%]	53.7% [48.9%, 58.3%]
Stage III	Any adjuvant chemotherapy & Clavien-Dindo Classification Grade I or lower	90.6% [88.5%, 92.4%]	74.7% [71.7%, 77.5%]	61.1% [57.7%, 64.3%]	48.6% [45.1%, 52.0%]
	Any adjuvant chemotherapy & Clavien-Dindo Classification Grade II or higher	84.2% [77.6%, 88.9%]	69.5% [61.8%, 76.0%]	61.6% [53.5%, 68.7%]	49.2% [41.0%, 56.8%]
	Surgery alone & Clavien-Dindo Classification Grade I or lower	73.9% [71.4%, 76.1%]	51.5% [48.7%, 54.2%]	39.3% [36.5%, 42.0%]	27.1% [24.6%, 29.7%]
	Surgery alone & Clavien-Dindo Classification Grade II or higher	64.7% [60.1%, 68.8%]	41.8% [37.1%, 46.3%]	34.6% [30.1%, 39.1%]	21.6% [17.7%, 25.7%]

Figure 6. Overall survival of all and age 75 or older patients at stage II or III by Clavien-Dindo classification and adjuvant chemotherapy. (A) Overall survival of all patients at stage II by Clavien-Dindo classification and adjuvant chemotherapy, **(B)** Overall survival of all patients at stage III by Clavien-Dindo classification and adjuvant chemotherapy, **(C)** Overall survival of age 75 or older patients at stage II by Clavien-Dindo classification and adjuvant chemotherapy, **(D)** Overall survival of age 75 or older patients at stage III by Clavien-Dindo classification and adjuvant chemotherapy.

anastomotic leakage, and intra-abdominal infection were other frequent complications. We recommend D2 lymphadenectomy as the standard surgical approach for patients with resectable gastric cancer because it is associated with a lower relapse rate and similar morbidity (*30-35*). Males are generally more susceptible than females to bacterial infections, and surgical site infection was also a risk factor for loss of lean body mass (*36,37*), which would decrease the compliance with S-1 treatment in the adjuvant setting after D2 lymphadenectomy (*36*). There was no difference in the incidence of postoperative complications between D1 and D2 in this retrospective study, although postoperative weight was not recorded in this registry. Laparoscopic surgery, which was an independent favorable prognostic factor compared with open surgery in this study, should be considered for elderly patients to improve their prognosis (*38*).

S-1 is an oral fluorouracil antitumor drug that combines tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP, which inhibits dihydropyrimidine dehydrogenase), and potassium oxonate (Oxo). CDHP clearance is delayed in patients with renal dysfunction, leading to a high AUC of 5-FU (*39*). Patients with creatinine clearance less than 60 mL/min are at significant risk of discontinuing S-1 in an adjuvant setting (*40*). Food intake affects the pharmacokinetics of Oxo but not of FT, CDHP, and 5-FU. Oxo exposure, which protects against gastrointestinal toxicity, is reduced under fed conditions compared to fasting conditions. Insufficient oral intake after gastrectomy leads to reduced levels of plasma Oxo, which in turn can engender diarrhea due to mucosal injury (*41-43*). Total gastrectomy significantly increased the maximum concentration and the area under the curve of plasma 5-FU and CDHP, which caused delayed clearance (*44*). Consistent with a previous study (*45*), we also found that patients who underwent total gastrectomy or those with a low creatinine clearance level tended to require dose reduction. The compliance of adjuvant chemotherapy was significantly worse in aged 75 or older, abnormal renal function, preoperative ECOG-PS 1 or more, total gastrectomy, stage III, and C-D II or more in this study. In age 75 or older patients, the compliance of adjuvant chemotherapy was significantly better in patients with normal renal function, preoperative ECOG-PS 0, D2 lymphadenectomy, except total gastrectomy, stage II in this study. Proximal gastrectomy, pylorus-preserving gastrectomy, or other ways to avoid total gastrectomy should be considered for some patients age 75 or more, as this could avert problems associated with reduced food intake and increased plasma 5-FU concentration.

The Maruyama Index (MI), an algorithm calculated

Table 4. Predictive factors of postoperative complication and compliance of adjuvant chemotherapy

Factors	Objective variant	*n*	Variant	Coefficient	95% CI (lower)	95% CI (upper)	*p*-value
Postoperative complication							
Overall patients	Clavien-Dindo classification	13,051	Constant	-2.07	-2.23	-1.92	< 0.001
	(Grade II or more *vs.* others)	13,051	Age ≥ 75 (*vs.* <75)	0.33	0.22	0.43	< 0.001
		13,051	Male (*vs.* female)	0.44	0.34	0.55	< 0.001
		13,051	Abnormal CCr (*vs.* Normal CCr)	0.15	0.04	0.26	0.006
		13,051	ECOG-PS 0 (*vs.* 1 or more)	-0.39	-0.48	-0.29	< 0.001
		13,051	D2 lymphadenectomy (*vs.* D1)	0.01	-0.09	0.11	0.844
		13,051	Total gastrectomy (*vs.* others)	0.45	0.36	0.55	< 0.001
		13,051	pStage III (*vs.* pStage II)	0.07	-0.02	0.16	0.123
Age ≥ 75	Clavien-Dindo classification	4,936	Constant	-1.52	-1.76	-1.29	< 0.001
	(Grade II or more *vs.* others)	4,936	Male (*vs.* female)	0.45	0.29	0.60	< 0.001
		4,936	Abnormal CCr (*vs.* Normal CCr)	0	-0.18	0.18	0.982
		4,936	ECOG-PS 0 (*vs.* 1 or more)	-0.39	-0.53	-0.25	< 0.001
		4,936	D2 lymphadenectomy (*vs.* D1)	-0.08	-0.22	0.06	0.236
		4,936	Total gastrectomy (*vs.* others)	0.28	0.14	0.42	< 0.001
		4,936	pStage III (*vs.* pStage II)	0.12	-0.02	0.26	0.091
Compliance of adjuvant chemotherapy							
Overall patients	Adjuvant chemotherapy	6,757	Constant	0.98	0.80	1.16	< 0.001
	(Completion *vs.* others)	6,757	Age ≥ 75 (*vs.* <75)	-0.42	-0.56	-0.29	< 0.001
		6,757	Male (*vs.* female)	-0.05	-0.16	0.06	0.359
		6,757	Abnormal CCr (*vs.* Normal CCr)	-0.53	-0.64	-0.42	< 0.001
		6,757	ECOG-PS 0 (*vs.* 1 or more)	0.23	0.11	0.34	< 0.001
		6,757	D2 lymphadenectomy (*vs.* D1)	0.10	-0.03	0.23	0.118
		6,757	Total gastrectomy (*vs.* others)	-0.42	-0.53	-0.32	< 0.001
		6,757	pStage III (*vs.* pStage II)	-0.36	-0.46	-0.25	< 0.001
		6,757	Clavien-Dindo classification Grade II or more (*vs.* others)	-0.21	-0.36	-0.06	0.007
Age ≥ 75	Adjuvant chemotherapy	1,298	Constant	0.51	0.12	0.90	0.010
	(Completion *vs.* others)	1,298	Male (*vs.* female)	-0.02	-0.26	0.22	0.899
		1,298	Abnormal CCr (*vs.* Normal CCr)	-0.58	-0.84	-0.32	< 0.001
		1,298	ECOG-PS 0 (*vs.* 1 or more)	0.31	0.08	0.53	0.009
		1,298	D2 lymphadenectomy (*vs.* D1)	0.28	0.02	0.54	0.032
		1,298	Total gastrectomy (*vs.* others)	-0.51	-0.75	-0.28	< 0.001
		1,298	pStage III (*vs.* pStage II)	-0.50	-0.73	-0.26	< 0.001
		1,298	Clavien-Dindo classification Grade II or more (*vs.* others)	-0.20	-0.52	0.12	0.210

Abbreviations: CCr, creatinine clearance; D1, D1 lymphadenectomy; ECOG-PS, Eastern Cooperative Oncology Group - performance status.

using preoperative patient characteristics such as age, sex, Borrmann type, presumed depth of the primary tumor, tumor location, maximum tumor diameter, and histologic type, estimates nodal metastatic status preoperatively to optimize lymphadenectomy. The MI was an independent predictor of both OS and disease-specific survival in a Dutch trial (*46-48*). Additionally, surgery in patients with a low MI was associated with enhanced regional control and survival, but did not alter the incidence of isolated distant metastases. We suggest that artificial intelligence that incorporates measurements such as the MI, pre-operative patient status and expected operative methods could facilitate personalized treatments including postoperative chemotherapy.

We observed that CY1 was associated with significantly reduced OS. Although S-1 monotherapy is recommended for CY1 gastric cancer after gastrectomy in Japanese Guidelines (*18,49*), its efficacy is questionable. Negative cytology following neoadjuvant chemotherapy has previously been associated with significantly improved OS in previous meta-analysis (*50*). Postoperative chemotherapy was clearly effective for CY1-positive gastric cancer cases in this study as well as adjuvant and metastatic setting, and we therefore strongly recommend this treatment for these patients.

There was no comparable previous big data analysis worldwide to analyze postoperative chemotherapy of gastric cancer. All patients underwent gastrectomy in Japanese hospitals and the most administered drug postoperatively was S-1 monotherapy as Japanese standard treatment in this retrospective study. Potential biases would not be excluded completely by the adjustment of considerable prognostic factors of the propensity score matching.

Conclusion

We found that although adjuvant chemotherapy was effective in elderly patients, they did tend to have a worse prognosis than younger patients. One of the main modifiable predictors of postoperative complications and lower compliance with adjuvant chemotherapy was total gastrectomy. Subtotal gastrectomy and total gastrectomy are recommended mainly as the standard procedure for resectable gastric cancer at stage II and III by the Japanese Gastric Cancer Treatment Guidelines. Through shared decision making among patients, doctors, and medical staff, proximal gastrectomy and pylorus-preserving surgery in addition to distal gastrectomy should therefore be considered to improve survival and quality of life for elderly patients. Additionally, segmental gastrectomy or local resection instead of total gastrectomy should be evaluated in clinical trials. Particular attention should be paid to proximal and distal margins in this case, because a poor post-surgery outcome cannot be rectified by adjuvant chemotherapy.

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Conflict of Interest: Yamada Y, Seto Y, Kodera Y, Doki Y, Yoshida K, Kumamaru H, Tachimori H, Sasako M, Katai H, Konno H have no conflicts of interest to disclose. Yoshikawa T has received honoraria from Chugai, Taiho, Daiichi Sankyo, Ono, Medtronic, Bristol-Myers Squibb (BMS), Janssen, AstraZeneca, Intuitive Surgical, Olympus, Astellas, Terumo, research funding from Lilly, and advisory role for MSD. Takeuchi H has received research funding and honoraria from Taiho. Kitagawa Y has received research funding and honoraria from Chugai, Taiho, honoraria from Kyowa Kirin, BMS, Nippon Kayaku, MSD, research funding from Ono, Daiichi Sankyo, Takeda. Muro K has received honoraria from BMS, Ono, MSD, Taiho, Takeda, Daiichi Sankyo, Eli Lilly, and research funding from Astellas, Amgen, Sanofi, Novartis, Parexel International, PRA Health Sciences, Taiho, MSD, Chugai, and Ono. Kabeya Y and Kamada A are employees of IBM Japan. Nagashima K received consulting and advisory fees from SENJU Pharmaceutical, Toray Industries, and Kowa Company. Kakeji Y has received research funding and honoraria from Taiho.

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**Address correspondence to*:
Yasuhide Yamada, Department of Medical Research, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: yayamada@hosp.ncgm.go.jp