Adjuvant Chemoradiation with 5-Fluorouracil/Leucovorin *versus* S-1 in Gastric Cancer Patients Following D2 Lymph Node Dissection Surgery: A Feasibility Study

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Abstract. *Purpose: We retrospectively analyzed the feasibility and adverse events for two regimens, postoperative chemoradiation (CRT) with 5-fluorouracil/leucovorin (5-FU/LV) compared to S-1 in D2-resected gastric cancer patients. Patients and Methods: The study included 405 gastric cancer patients who underwent curative gastrectomy with D2 lymph node dissection and received adjuvant therapy between January 2008 and July 2009. Feasibility and adverse events for the CRT and S-1 regimens were analyzed. Results: Out of the 405 patients, 244 (60.2%) had CRT and 161 (39.8%) had S-1 treatment. The regimen was selected based on the preferences of the physician and the patient. S-1 was more frequently administered to patients with older age (age ≥70) and those with early-stage disease (stage II). The stage was significantly more advanced in the CRT group compared to the S-1 group (S-1 vs. CRT: stage II, 59.6% vs. 36.1%; stage III/IV, 28.0% vs. 48.3%, respectively; p<0.001). The completion rate of the planned therapy was significantly higher in the CRT group than in the S-1 group (95.1% vs. 72.8%, respectively; p<0.001). Regarding severe adverse events (grade 3-4), neutropenia (CRT vs. S-1; 40.2% vs. 8.7%, respectively, p<0.001), nausea (CRT vs. S-1; 5.7% vs. 0%, respectively; p=0.002) and stomatitis (CRT vs. S-1; 7.4% vs. 2.5%, respectively; p=0.034) were significantly more frequent in the CRT cohort compared to the S-1 group. Conclusion: Both adjuvant CRT with 5-FU/LV and adjuvant S-1 are safe and feasible in D2-resected gastric cancer patients. Patients with old age or early stage disease tend to prefer S-1 therapy to chemoradiation.*

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Gastric cancer (GC) is the fourth most common type of cancer and the second most common cause of cancer-related death worldwide (1, 2). Surgery is the only curative treatment for gastric cancer. However, even after a complete surgical resection a considerable number of patients experience recurrence and require palliative therapy (3, 4). Several meta-analyses have shown that adjuvant chemotherapy has beneficial effects in patients with gastric cancer (5-7). Moreover, two randomized controlled phase III clinical trials showed that adjuvant therapy reduced recurrence and prolonged survival (8, 9).

One of the landmark adjuvant trials was the INT-0116 (intergroup 0116) study (9), which demonstrated a definite survival benefit with chemoradiation (CRT) in patients with gastric cancer with 3-year overall survival rates of 50% and 41% for the postoperatively-treated and surgery-only groups, respectively (9). Since the results of the INT-0116 study were reported in 2001, CRT has been considered a standard-of-care in the United States (10, 11) where D1 lymph node dissection is the standard surgical procedure. Furthermore, an observational study in our Institute (12, 13) suggested that postoperative CRT with the INT-0116 regimen decreased recurrence and prolonged survival in patients with gastric cancer who undergo D2 lymph node dissection.

In 2007, results of the adjuvant chemotherapy trial of the oral fluoropyrimidine, S-1 for gastric cancer (ACTS-GC) (8)

in Japan were published. These showed that adjuvant S-1 treatment for 1 year following curative gastrectomy with D2 lymph node dissection increased both relapse-free survival and overall survival in pathological stage II and III gastric cancer (8). Thereafter, both CRT and S-1 were accepted as adjuvant therapy for gastric cancer. Because there is no direct comparison of CRT and S-1 chemotherapy in D2-resected GC patients in terms of feasibility, tolerability and efficacy, we designed this study to compare S-1 versus CRT with 5-fluorouracil/leucovorin (5-FU/LV) as adjuvant treatment in D2-dissected GC patients.

Patients and Methods

We retrospectively reviewed the medical records of all patients who had received adjuvant CRT therapy or S-1 chemotherapy following curative resection with D2 lymph node dissection for gastric cancer at the Samsung Medical Center between January 2008 and July 2009. Patients met the following criteria: (i) pathologic stage IB, II, IIIA, IIIB or IV (M0) gastric cancer as defined by the American Joint Committee on Cancer (AJCC) staging system 6th edition, (ii) Eastern Cooperative Oncology Group (ECOG) performance status 0-2. This study was approved by the institutional review board of Samsung Medical Center.

Surgery. The surgical requirement for eligibility was curative resection and *en bloc* resection of the tumor with negative margins. All patients had undergone extensive (D2) lymph node dissection. This procedure involves the resection of all perigastric nodes and some celiac, splenic or splenic-hilar, hepatic artery and cardial lymph nodes, depending on the location of the tumor.

Adjuvant treatment. Adjuvant treatment was discussed in the Division of Oncology upon receiving the pathologic staging report after surgery. Based on evidence documented in the literature, the adjuvant treatment modalities available during the study period were CRT or S-1 (8, 11). Both adjuvant treatment regimens were explained to the patients and the final choice of regimen was based on a shared decision process among the patient, the patient's family and the oncologist taking into consideration several factors including medical condition, co-morbidities, recovery state, oral intake and age. Adjuvant CRT or S-1 was started 3-8 weeks after surgery.

For the CRT group, the schedule was adopted from the INT 0116 protocol (Southwest oncology group (SWOG)) (9, 12). Chemotherapy for 5 days with 5-fluorouracil (5-FU, 400 mg/m^2/day) and leucovorin (LV, 20 mg/m^2/day) was started on day 1 and followed by chemoradiotherapy beginning 28 days after the start of the initial cycle of chemotherapy. CRT consisted of 4,500 cGy of radiation at 180 cGy/day given 5 days/week for 5 weeks, with 5-FU and LV on the first 4 and the last 3 days of radiotherapy. One month after the completion of radiotherapy, two 5-day cycles of 5-FU plus LV were administered 1 month apart. Planned total doses of LV and 5-FU were 440 mg/m^2 and 8,800 mg/m^2, respectively.

For the S-1 group, oral S-1 (40 mg/m^2) was administered twice daily for 4 weeks followed by 2 weeks of rest for a maximum of eight cycles every 6 weeks for 1 year (8). The S-1 dose was proportional to patients' body surface area (14). The dose of 5-FU or S-1 was reduced at the physician's discretion in patients who had grade 3 or 4 hematological adverse events or grade 2-4 non-hematological adverse events. Adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE version 3.0) (15).

Evaluation and follow-up. Complete blood counts and serum chemistry were performed before every cycle. Abdominopelvic computed tomography (CT) was performed after four cycles of S-1 chemotherapy and after five cycles of 5-FU/LV/RT. Follow-up of both groups occurred at 6-month intervals for five years and yearly thereafter. Follow-up consisted of physical examination, complete blood count, chemistry, chest radiography, abdominopelvic CT and gastroscopy. During the follow-up period, any suspected recurrence was confirmed by biopsy. However, cases with definite recurrent lesions in abdominopelvic CT and/or chest CT or other imaging modalities including bone scan or positron emission tomography-computed tomography (PET-CT) were defined as recurrence without histological confirmation.

Statistical methods. The χ^2 test or Fisher's exact test was used to compare the two study groups. Disease-free survival (DFS) was calculated as the period from the date of surgery to the date of recurrence or death of any cause. Overall survival (OS) was defined as the period from the date of surgery to the date of death of any cause or the last follow-up date. DFS and OS were estimated by the Kaplan-Meier product limit method. The log-rank test was used to compare survival rates. A p-value <0.05 was considered significant. A Cox proportional hazards regression model was used to assess the effect of each potential predictive variable on the DFS and OS. All statistical analyses were performed with the SPSS, version 18.0 (Chicago, IL, USA).

Results

Patients' characteristics. Between January 2008 and July 2009, 405 patients met the eligibility criteria and were referred to the Division of Oncology for consultation on adjuvant chemotherapy. Of the 405 patients, 244 (60.2%) received adjuvant CRT and 161 (39.8%) received adjuvant S-1 chemotherapy. The clinical characteristics of the patients in the two groups are summarized in Table I. The patients' age was significantly younger in the CRT cohort (median age=53 years, range=24-76) compared with the S-1 group (57 years, range=27-80) ($p=0.001$). Of note, the percentage of patients with age >70 years was considerably higher in the S-1 group (14.8%) *vs*. CRT (4.1%) with statistical significance ($p<0.001$). The proportion of patients with stage III/IV disease was significantly higher in the CRT cohort than in the S-1 group (CRT *vs*. S-1; stage IB-II, 51.6% *vs*. 72.0%; stage III-IV, 48.4% *vs*. 28.0%, respectively). The number of involved lymph nodes was higher in the CRT group with statistical significance. There was no significant difference between the two groups regarding the type of surgery and histology (Table I).

Treatment delivered. Overall, the completion rate was substantially higher in the CRT group (232/244, 95.1%) than in the S-1 group (118/161, 73.3%) ($p<0.001$) (Table II).

Table I. *Patients' characteristics*.

	CRT (N=244)	S-1 (N=161)	Total (N=405)	*p*-Value
Age in years (median)	53 (24-76)	57 (27-80)	54 (24-80)	0.001
<70	234 (95.9%)	137 (85.1%)	371 (91.6%)	<0.001
≥70	10 (4.1%)	24 (14.8%)	34 (8.4%)	
Gender				0.219
Male	149 (61.1%)	108 (67.1%)	257 (63.5%)	
Female	95 (38.9%)	53 (32.9%)	148 (36.5%)	
ECOG PS				>0.999
0-1	243 (99.6%)	160 (99.4%)	403 (99.5%)	
2	1 (0.4%)	1 (0.6%)	2 (0.5%)	
T stage				0.020
Ia	8 (3.3%)	2 (1.2%)	10 (2.5%)	
Ib	26 (10.7%)	13 (8.1%)	39 (9.6%)	
2a	42 (17.2%)	45 (28.0%)	87 (21.5%)	
2b	97 (39.8%)	72 (44.7%)	169 (41.7%)	
3	64 (26.2%)	27 (16.8%)	91 (22.5%)	
4	7 (2.9%)	2 (1.2%)	9 (2.2%)	
No. of LN metastases				<0.001
0	21 (8.6%)	12 (7.5%)	33 (8.1%)	
1-6	115 (47.1%)	113 (70.2%)	228 (56.3%)	
7-15	66 (27.0%)	28 (17.4%)	94 (23.2%)	
≥16	42 (17.2%)	8 (5.0%)	50 (12.3%)	
Stage				<0.001
IB	38 (15.6%)	20 (12.4%)	58 (14.3%)	
II	88 (36.1%)	96 (59.6%)	184 (45.4%)	
IIIA	53 (21.7%)	29 (18.0%)	82 (20.2%)	
IIIB	19 (7.8%)	7 (4.3%)	26 (6.4%)	
IV	46 (18.9%)	9 (5.6%)	55 (13.6%)	
Type of resection				
Total gastrectomy	84 (34.4%)	55 (34.2%)	139 (34.3%)	>0.999
Subtotal gastrectomy	159 (65.2%)	106 (65.8%)	265 (65.4%)	
Proximal resection	1 (0.4%)	0 (0%)	1 (0.2%)	
Histology				0.234
Tubular adenocarcinoma	167 (68.4%)	108 (67.1%)	275 (67.9%)	
Mucinous adenocarcinoma	6 (2.5%)	11 (6.8%)	17 (4.2%)	
Signet ring cell carcinoma	54 (22.1%)	34 (21.1%)	88 (21.7%)	
Papillary adenocarcinoma	9 (3.7%)	3 (1.9%)	12 (3.0%)	
Others	8 (3.3%)	5 (3.1%)	13 (3.2%)	

CRT, Chemoradiation; LN, lymph node; ECOG PS, Eastern Cooperative Oncology Group performance status.

Moreover, 21 (13.0%) of 161 patients receiving S-1 stopped treatment during their course of chemotherapy because of patient refusal. All patient refusals were due to financial issues because expenses for S-1 were not reimbursed by the Health Insurance Review and Assessment Service (HIRA) in Korea during the study period.

Toxicity. The incidence of grade 3/4 neutropenia was considerably higher in the CRT group (40.2%) compared to the S-1 group (8.7%) with statistical significance ($p<0.001$) (Table III); however, most episodes of neutropenia spontaneously recovered after a delay in chemotherapy. The incidence of neutropenic fever was 2.9% (7/244) in the CRT group compared to no cases in the S-1 group ($p=0.045$) (Table III). The non-hematological toxicity profile differed between the two cohorts. As expected, the frequency of grade 3 nausea was substantially higher in the CRT group (14/244, 5.7%) than in the S-1 group (0/162, 0%) ($p=0.002$). The frequency of grade 3 stomatitis was also higher in the CRT group (18/244, 7.4%) than in the S-1 group ($p=0.034$). Grade 3/4 hyperbi-lirubinemia showed a higher incidence in the S-1 group (6/161, 3.7% in S-1 *vs*. 0/244, 0% in CRT; $p=0.004$). However, after dose reduction hyperbilirubinemia did not recur in subsequent cycles and all of the hyperbilirubinemia events spontaneously recovered upon cessation of S-1 chemotherapy.

Recurrence and survival. After a median follow-up of 49.0 months (range=3.0-62.0 months) there were 99 recurrences

Table II. *Reasons for the cessation of adjuvant therapy.*

	CRT (N=244)	S-1 (N=161)	Total (N=405)	*p*-Value
Protocol treatment completed	232 (95.1%)	118 (73.3%)	350 (86.4%)	<0.001
Intolerable adverse events	9 (3.7%)	11 (6.8%)	20 (4.9%)	0.153
Patients' refusal	0 (0%)	21 (13.0%)	21 (5.2%)	<0.001
Recurrence of disease	2 (0.8%)	10 (6.2%)	12 (3.0%)	0.002
Other causes*	1 (0.4%)	1 (0.6%)	2 (0.5%)	>0.999

* Operation for thoracic aorta aneurysm rupture in CRT group, Work-up for recurrence in S-1 group; CRT, chemoradiation

Table III. *Adverse events, according to treatment group.*

Hematological toxicities

	CRT (N=244)			S-1 (N=161)			*p*-Value
Grade	3	4	3-4	3	4	3-4	
Anemia	5	0	5(2.0%)	0	0	0	0.162
Neutropenia	74	24	98 (40.2%)	13	1	14 (8.7%)	<0.001
Thrombocytopenia	0	0	0	0	0	0	
FN	7	0	7 (2.9%)	0	0	0	0.045

Non-hematological toxicities

	CRT (N=244)				S-1 (N=161)				*p*-Value
Grade	1	2	3	4	1	2	3	4	
AST/ALT elevation	19	12	2 (0.8%)	0	0	2	1 (0.6%)	0	1.000
Jaundice	0	9	0	0	0	13	6 (3.7%)	0	0.004
Anorexia	20	30	2 (0.8%)	0	38	29	5 (3.1%)	0	0.120
Nausea	42	28	14 (5.7%)	0	37	11	0	0	0.002
Vomiting	9	7	6 (2.5%)	0	3	0	0	0	0.085
Diarrhea	25	14	9 (3.7%)	0	25	15	5 (3.1%)	0	0.753
Stomatitis	26	22	18 (7.4%)	0	15	5	4 (2.5%)	0	0.034
Fatigue	2	8	1 (0.4%)	0	6	6	2 (1.2%)	0	0.566
Rash	1	4	1 (0.4%)	0	8	2	1 (0.6%)	0	1.000
Skin pigmentation	5	0	0	0	12	0	0	0	
Hand-foot syndrome	2	2	0	0	13	2	1 (0.6%)	0	0.398
Alopecia	12	0	0	0	5	0	0	0	

CRT, Chemoradiation; FN, febrile neutropenia; AST/ALT, aspartate aminotransferase/alanine aminotransferase.

overall (70 in the CRT group (28.7%) and 29 in the S-1 group (18.0%); p=0.014). The estimated 3-year DFS rates were 73.0% in the CRT group and 81.4% in the S-1 group (p=0.035) (Figure 1A). In multivariate analysis with stage and treatment group, the type of adjuvant therapy had no effect on RFS (p=0.844 in stage Ib-II group, p=0.506 in stage III-IV group) (Figure 1B, 1C) (Table IV). During follow-up 87 patients died, with estimated 3-year OS rates of 79.8% in the CRT group and 87.7% in the S-1 group.

Table IV. *Multivariate analysis for recurrence-free survival.*

	Hazard Ratio	95% CI for Exp(B)	*p*-Value
Regimen: S-1/CRT	0.769	0.500-1.185	0.234
Stage: III-IV/Ib-II	4.154	2.692-6.409	<0.001
Age: ≥70/<70	2.312	1.278-4.184	0.006
Op extent: TG/STG	1.396	0.946-2.062	0.093

CRT, Chemoradiation; CI, confidence interval; Op extent, operation extent; TG/STG, total gastrectomy/subtotal gastrectomy.

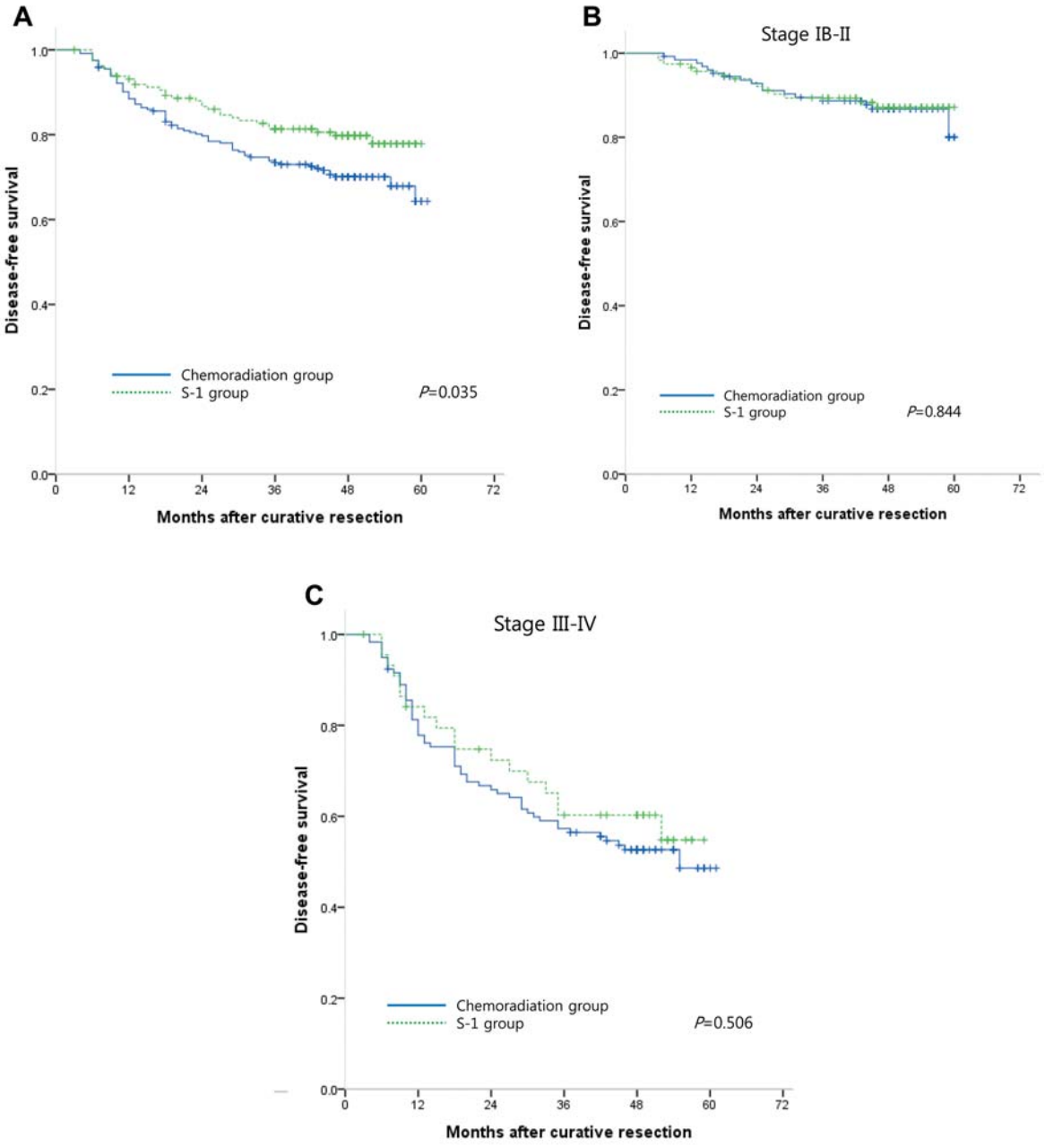

Figure 1. *A. Comparison of overall disease-free survival in chemoradiation (CRT) and S-1 groups; B. and C. Comparison of disease-free survival (DFS) in CRT and S-1 groups by staging.*

Discussion

In the present retrospective analysis we compared, for the first time, the tolerability of CRT (INT 0116) and S-1 as adjuvant treatment in D2-resected GC patients. During the study period, CRT with 5-FU/LV and S-1 chemotherapy were the only regimens approved for prescription based on evidence from phase III trials.

Approximately 40% of patients chose S-1 therapy; in particular, patients with older age, early-stage disease or fewer lymph node metastases tended to prefer the S-1 therapy to CRT. This decision was based on the preference of the physician and patients, while the type of resection had no influence on the choice of adjuvant therapy. A high proportion (95.1%) of patients in the CRT group completed the planned 5 months of treatment and 73.3% of patients in

the S-1 group completed the planned 1 year of treatment. The completion rate of the S-1 group is consistent with previous Japanese and Korean studies (8, 16-18). The lower rate of completion in the S-1 group was most likely because of insurance problems and the longer duration of treatment. Interestingly, although severe adverse events were more frequent in the CRT group, this did not result in cessation of treatment. In comparison with the completion rate of the INT-0116 study (64%), our patients who selected CRT actually showed a high compliance rate.

In the CRT group, grade 3-4 neutropenia was detected in 98 patients (40.2%) but only 7 (2.9%) experienced febrile neutropenia (FN). Rates of grade 3-4 stomatitis (N=18, 7.4%) and nausea (N=14, 5.7%) were significantly higher in the chemoradiation group than in the S-1 group. This toxicity profile is compatible with that reported in the INT-0116 study (Grade 3-4 hematologic toxicities 54%, gastrointestinal toxicities 33%) (9). In the S-1 group the only grade 3-4 hematological toxicity was neutropenia (N=14, 8.7%); this occurred at a significantly lower rate than in the CRT group ($p<0.001$) and there were no cases of FN. Grade 3-4 non-hematological toxicities were jaundice (N=6, 3.7%), anorexia or diarrhea (N=5, 3.1%) and stomatitis (N=4, 2.5%). The toxicity profiles of the S-1 group are consistent with those of several previous Japanese studies and one Korean study (8, 16-19), which reported rates of 5.0-29.0% for grade 3-4 neutropenia, 2.0-9.7% for diarrhea, 3.0-9.7% for anorexia and 1.0-2.0% for jaundice.

Our results support findings of the INT-0116 study and the ACTS-GC trial that indicated efficacy of CRT and S-1, respectively, as adjuvant treatments for patients with D2-ressected GC. Although addition of RT to chemotherapy did not significantly reduce recurrence in the ARTIST trial (20), in sub-group analysis the addition of RT prolonged DFS in pathological lymph node-positive GC. A clinical trial involving only pathologic lymph node-positive disease is currently ongoing (ARTIST II; S-1 *vs*. S-1/oxaliplatin *vs*. S-1/oxaliplatin/RT group).

In conclusion, our study indicated that both adjuvant CRT and S-1 therapy are safe and feasible in Korean patients with D2-dissected gastric cancer. The ARTIST II trial is expected to give us more information about adjuvant treatment in gastric cancer.

Conclusion

Both adjuvant CRT with 5-FU/LV and adjuvant S-1 are safe and feasible in D2-resected gastric cancer patients. Patients with older age or early-stage disease tend to prefer S-1 therapy to chemoradiation.

Conflicts of Interest

None.

Acknowledgements

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