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ORIGINAL ARTICLE

Role of reduction gastrectomy in patients with gastric cancer with a single non-curable factor: Supplementary analysis of REGATTA trial

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Abstract

Background: REGATTA trial failed to demonstrate the survival benefit of reduction gastrectomy in patients with advanced gastric cancer with a single non-curable factor. However, a significant interaction was found between the treatment effect and tumor

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location in the subset analysis. Additionally, the treatment effect appeared to be different between Japan and Korea. This supplementary analysis aimed to elucidate the effect of reduction surgery based on tumor location and country.

Methods: Multivariable Cox regression analyses in each subgroup were performed to estimate the hazard ratio (HRadj), including the following variables as explanatory variables: country, age, sex, incurable factor, cT, cN, primary tumor, performance status, histological type, and macroscopic type.

Results: Patients (95 in Japan and 80 in Korea) were randomized to chemotherapy alone (86 patients) or gastrectomy plus chemotherapy (89 patients). The subgroup analysis according to the country revealed a worse overall survival in gastrectomy plus chemotherapy arm in Japan (hazard ratio: 1.32, 95% confidence interval: 0.85–2.05), but not in Korea (hazard ratio: 0.85.95% confidence interval: 0.52–1.40). Overall survival was better in distal gastrectomy plus chemotherapy compared with chemotherapy alone (hazard ratio = 0.69, 95% confidence interval: 0.42–1.13), and worse in total gastrectomy plus chemotherapy compared with chemotherapy alone (hazard ratio = 1.34, 95% CI: 0.93–1.94), which was more remarkable in Korea than in Japan.

Conclusions: Primary chemotherapy is a standard of care for advanced gastric cancer; however, the survival benefits from reduction by distal gastrectomy remained controversial.

KEYWORDS
distal gastrectomy, gastric cancer, palliative surgery, reduction gastrectomy

1 | INTRODUCTION

Chemotherapy is the standard of care for incurable advanced gastric cancer. REGATTA JCOG0705/KGCA01, which investigated the survival benefit of reduction gastrectomy in patients with advanced gastric cancer with a single non-curable factor, failed to demonstrate the superiority of gastrectomy plus chemotherapy over chemotherapy alone.[1]

However, the subgroup analysis showed an interaction between the treatment effect and tumor location. Additionally, treatment effects were different between Japan and Korea. The efficacy and tolerability of chemotherapy have been reported as nearly equivalent between Japan and Korea,[2] but other factors, such as the number of treatment cycles, are speculated to affect patient survival.

Thus, this supplementary analysis aimed to explore the subgroups for which reduction gastrectomy might be beneficial with special reference to the tumor location and the country.

2 | METHODS

2.1 | Study design and patients

REGATTA was an open-labeled, randomized, phase 3 trial conducted by the Japan Clinical Oncology Group (JCOG; JCOG0705) and the Korean Gastric Cancer Association (KGCA; KGCA01). The study design and inclusion criteria were previously published in detail.[1] Briefly, patients aged 20–75 years with histologically proven primary gastric adenocarcinoma with a single non-curable factor were included. A single non-curable factor was defined as follows: hepatic metastasis (H1; 2–4 lesions with a maximum diameter of ≤5 cm and a minimum diameter of ≥1 cm), peritoneal metastasis (P1) in the diaphragm or peritoneum caudal to the transverse colon without massive ascites or intestinal obstruction, and para-aortic lymph node metastasis of a maximum diameter of ≥1 cm (M1 LYM) above the celiac axis and/or below the inferior mesenteric artery (lymph node 16a1/b2 according to the Japanese classification of gastric carcinoma).[3] Tumors were staged under the Second English Edition of the Japanese classification of gastric carcinoma.[2] Patients with insufficient oral intake or active bleeding from the gastric tumor were excluded.

The study protocol of JCOG0705/KGCA01 was approved by the JCOG Protocol Review Committee and the institutional review board of each participating hospital before the study initiation. JCOG0705/KGCA01 was done following the international ethical recommendations stated in the Declaration of Helsinki, Japanese Ethical Guidelines for Clinical Research, and Guideline for Korean Good Clinical Practice. Patients provided written informed consent before enrollment. JCOG0705/KGCA01 is registered with UMIN-CTR, number UMIN000001012.

2.2 | Randomization

Eligible patients were registered and randomly assigned (1:1) to chemotherapy alone arm or gastrectomy plus chemotherapy arm in each country using a minimization method with a biased-coin assignment to balance the groups based on institution, clinical nodal status (N0–1 vs. N2–3), and non-curable factor (hepatic, peritoneal vs. para-aortic metastasis).

2.3 | Treatments

The type of resection, associated D1 lymph node dissection, and total, distal, or proximal gastrectomy in patients assigned to the gastrectomy plus chemotherapy arm was determined by each investigator depending on tumor location and extension. Chemotherapy with S-1 plus cisplatin (SP),[4] which consisted of oral S-1 at 80 mg/m^2 per day on days 1–21 and cisplatin at 60 mg/m^2 on day 8 in a 5-week cycle, was started within 8 weeks postoperatively. Patients assigned to the chemotherapy alone arm received the same chemotherapy with SP. Palliative gastrectomy was allowed only when severe uncontrollable symptoms, such as bleeding and obstruction, emerged during chemotherapy.

2.4 | Outcomes

The primary endpoint was overall survival (OS), defined as the time from randomization to all-cause death. Secondary endpoints include progression-free survival and safety. Both gastrectomy-related complications and chemotherapy-related adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (version 3.0).

2.5 | Statistical analysis

JCOG0705/KGCA01 was designed to investigate the superiority of gastrectomy plus chemotherapy compared with chemotherapy alone in terms of OS. The planned sample size was 330 (165 per group), with a one-sided α error of 5% and statistical power of 80% to detect the difference in 2-year survival difference by 10% (20% with chemotherapy alone vs. 30% with gastrectomy plus chemotherapy). Initially, a 2-year follow-up was planned after complete patient accrual for 4 years. The protocol was amended on May 22, 2012, to prolong the total accrual period from 4 to 5.5 years with a 2-year follow-up because of slow patient accrual.

Two interim analyses were planned, considering adjustments for repeated comparisons with the Lan and DeMets method and the O'Brien-Fleming type α spending function.[5] The details for interim analysis were previously published.[1]

The first interim analysis was conducted on Sept 14, 2013, for 164 enrolled patients based on data as of June 3, 2013. The JCOG Data and Safety Monitoring Committee recommended early study termination according to the prespecified stopping criteria based on futility.[1]

Data from all randomized 175 patients were analyzed for OS on an intention-to-treat basis. Survival curves were estimated using the Kaplan–Meier method and compared using the stratified log-rank test with the country as a stratum. Hazard ratios (HRs) were estimated using a stratified Cox regression model with the country as a stratum. The present supplemental analysis performed multivariable Cox regression analyses in each subgroup to estimate the HR (HRadj), including the following explanatory variables: country, age, sex, incurable factor, cT, cN, primary tumor location, performance status (PS), histological type, and macroscopic type. Analyses were done using SAS version 9.2 or later.

3 | RESULTS

JCOG0705/KGCA01 enrolled 175 patients (95 in Japan and 80 in South Korea including one patient from Singapore) from February 4, 2008, to September 17, 2013, who were randomly assigned to chemotherapy alone arm (86 patients) or gastrectomy plus chemotherapy arm (89 patients) (Figure 1). Chemotherapy alone and gastrectomy plus chemotherapy arms have seven and one ineligible patients, respectively. Two patients from the gastrectomy plus chemotherapy

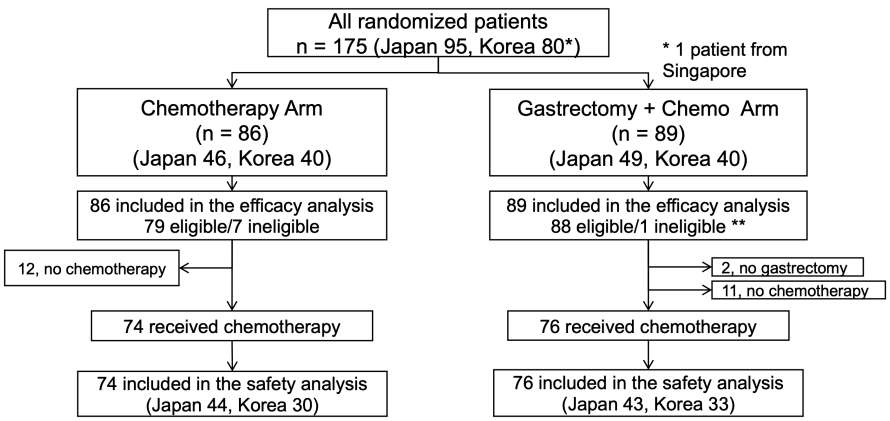

FIGURE 1 Consort diagram.

arm did not undergo gastrectomy. Planned chemotherapy was not delivered in 12 and 11 patients in the chemotherapy alone and gastrectomy plus chemotherapy arms, respectively.

Table 1 shows the patient characteristics according to tumor location in each country. Patients from Korea were approximately 10 years younger than Japan. The proportion of female sex was relatively higher in M-lesion in Japan and L-lesion in Korea. Macroscopic type 4 was more frequent in Japan, especially in U- and M-lesions. The gastrectomy plus chemotherapy arm had proximal gastrectomy in two, distal gastrectomy in 28, total gastrectomy in 57, exploratory laparotomy in one, and surgical refusal in one patient. All patients with U-lesion received total gastrectomy both in Korea and Japan. Similarly, approximately 70% of patients with M-lesions received total gastrectomy in both countries. However, more patients received distal gastrectomy in patients with L-lesion in Korea than in Japan.

The median OS was 16.6 months (95% confidence interval [CI]: 13.7–19.8) and 14.3 months (11.8–16.3) for patients assigned to chemotherapy alone and gastrectomy plus chemotherapy arms, respectively (HR: 1.09, 95% CI: 0.78–1.52; one-sided $p = 0.70$).[1] The subgroup analysis revealed a p-value of <0.05 in interactions with treatment effects in clinical N stage and tumor location. The effect of gastrectomy plus chemotherapy compared with chemotherapy alone on OS was significantly unfavorable in patients with N0–1 disease (HR: 1.79, 95% CI: 1.14–2.83; two-sided $p = 0.011$) and those with upper-third tumors (2.23, 1.14–4.37; two-sided $p = 0.017$).[1]

Figure 2 demonstrates the OS according to the treatment in each country. In Japan, survival in the chemotherapy alone arm was better than in the gastrectomy plus chemotherapy arm although without a statistically significant difference. On the contrary, survival curves were almost similar in Korea, where survival in the

TABLE 1 Patient characteristics according to tumor location in each country.

	U lesion		M lesion		L lesion	
	Japan ($n = 26$)	Korea ($n = 20$)	Japan ($n = 54$)	Korea ($n = 25$)	Japan ($n = 15$)	Korea ($n = 35$)
Age (years)	64 (62–68)	54 (47–58.5)	63 (57–68)	53 (48–60)	65 (58–72)	56 (50–67)
Sex						
Male	20 (77%)	14 (70%)	29 (54%)	18 (72%)	13 (87%)	23 (66%)
Female	6 (23%)	6 (30%)	25 (46%)	7 (28%)	2 (13%)	12 (34%)
Non-curable factor						
Liver metastasis (H1)	4 (15%)	1 (5%)	5 (9%)	1 (4%)	2 (8%)	3 (9%)
Peritoneal metastasis (P1)	18 (69%)	15 (75%)	41 (76%)	23 (92%)	10 (67%)	24 (69%)
Para-aortic lymph node metastasis (M1 LYM)	4 (15%)	3 (15%)	8 (15%)	0	3 (20%)	6 (17%)
Missing[a]	0	1 (5%)	0	1 (4%)	0	2 (6%)
Clinical tumor stage						
T2	3 (12%)	1 (5%)	7 (13%)	1 (4%)	2 (13%)	3 (9%)
T3	23 (88%)	19 (95%)	47 (87%)	24 (96%)	13 (87%)	32 (91%)
Clinical nodal stage						
N0-1	14 (54%)	9 (45%)	31 (57%)	16 (64%)	4 (27%)	18 (51%)
N2-3	12 (46%)	11 (55%)	23 (43%)	9 (36%)	11 (73%)	17 (49%)
Histological type[b]						
Intestinal	10 (38%)	0	15 (28%)	3 (12%)	5 (33%)	10 (29%)
Diffuse	16 (62%)	20 (100%)	39 (72%)	22 (88%)	10 (67%)	25 (71%)
Macroscopic type						
0–3 or 5	14 (54%)	16 (80%)	34 (63%)	19 (76%)	11 (73%)	32 (91%)
4	12 (46%)	4 (20%)	20 (37%)	6 (24%)	4 (27%)	3 (9%)
Operative procedures[c]						
Total gastrectomy	18 (100%)	11 (100%)	16 (70%)	5 (72%)	3 (43%)	4 (19%)
Distal gastrectomy	0	0	7 (30%)	1 (14%)	4 (57%)	16 (76%)
Proximal gastrectomy	0	0	0	1 (14%)	0	1 (5%)

Note: Data are median (IQR) or number (%). Some percentages do not add up to 100 because of rounding.

[a]Two patients without a non-curable factor and two patients who did not undergo laparoscopy or laparotomy.

[b]Based on the Lauren classification.

[c]In gastrectomy plus chemotherapy arm only.

gastrectomy plus chemotherapy arm was better after 24 months from randomization.

Further subgroup analysis according to the tumor location was performed (Figure 3), which revealed that the survival in the chemotherapy alone arm was better in Japan and Korea in tumors at U-lesion (Figure 3A–C). The survival between the treatment arms in both countries in tumors at M-lesion demonstrated no difference (Figure 3D–F). However, survival in the gastrectomy plus chemotherapy arm looks better in Korean patients with tumors at the L-lesion (Figure 3G–I).

The number of median chemotherapy cycles according to each subgroup (chemotherapy alone arm vs. gastrectomy plus chemotherapy arm) were 7 versus 3, 6 versus 5, and 4 versus 4.5 in Japan, and 6 versus 5.5, 8 versus 7, and 3 versus 6 in Korea in U-, M-, and L-lesions, respectively. The whole number of chemotherapy cycles (chemotherapy alone arm vs. gastrectomy plus chemotherapy arm) was 6 versus 4 in Japan and 6 versus 6 in Korea.

Patients in the gastrectomy plus chemotherapy arm were subdivided according to the resection type and compared with the chemotherapy alone arm (Figure 4). OS was better in patients who received distal gastrectomy plus chemotherapy compared with chemotherapy alone (HR = 0.69) and worse in patients who received total gastrectomy plus chemotherapy compared with chemotherapy alone (HR = 1.34). The survival in the chemotherapy alone arm was similar to that in patients who received distal gastrectomy plus chemotherapy in Japan. The survival in patients who received total gastrectomy plus chemotherapy was poorer than chemotherapy alone. However, survival in patients who underwent distal gastrectomy plus chemotherapy was better than chemotherapy alone in Korea. HR in distal gastrectomy plus chemotherapy versus chemotherapy alone was 0.53 (95% CI: 0.26–1.08).

HRadj showed a similar tendency to unadjusted HR suggesting the robustness of the results. HRadj was 1.10 (95% CI: 0.73–1.65) and 0.68 (95% CI: 0.36–1.28) in patients receiving total and distal gastrectomy, respectively. HRadj was as low as 0.40 (95% CI: 0.14–1.11) in Korean patients receiving distal gastrectomy.

The median number of chemotherapy cycles after distal and total gastrectomies in arm B was 4 and 3.5 in Japan and 6.5 and 6 in Korea, respectively.

Regarding postprotocol treatment, 38 (83%) and 38 (78%) patients in Japan and 32 (80%) and 27 (68%) patients in Korea in the chemotherapy alone arm and gastrectomy plus chemotherapy arm received second-line chemotherapy, respectively. The proportion of patients who received second-line chemotherapy based on the tumor location in U-, M-, and L-lesions (chemotherapy alone arm vs. gastrectomy plus chemotherapy arm) were 86% versus 84%, 87% versus 74%, and 63% versus 71% in Japan, and 89% versus 82%, 83% versus 86%, and 69% versus 55% in Korea, respectively. The proportion of patients who received second-line chemotherapy according to surgical type in gastrectomy plus chemotherapy arm after distal and total gastrectomies were 82% and 76% in Japan and 53% and 75% in Korea, respectively.

4 | DISCUSSION

The REGATTA trial, JCOG0705/KGCA01, was the first phase III trial to investigate the efficacy of reduction gastrectomy for metastatic gastric cancer globally.[1] Results denied the usefulness of reduction gastrectomy in patients with a single non-curable factor. However, the subgroup analysis suggested a different trend depending on countries and tumor locations; thus, we conducted

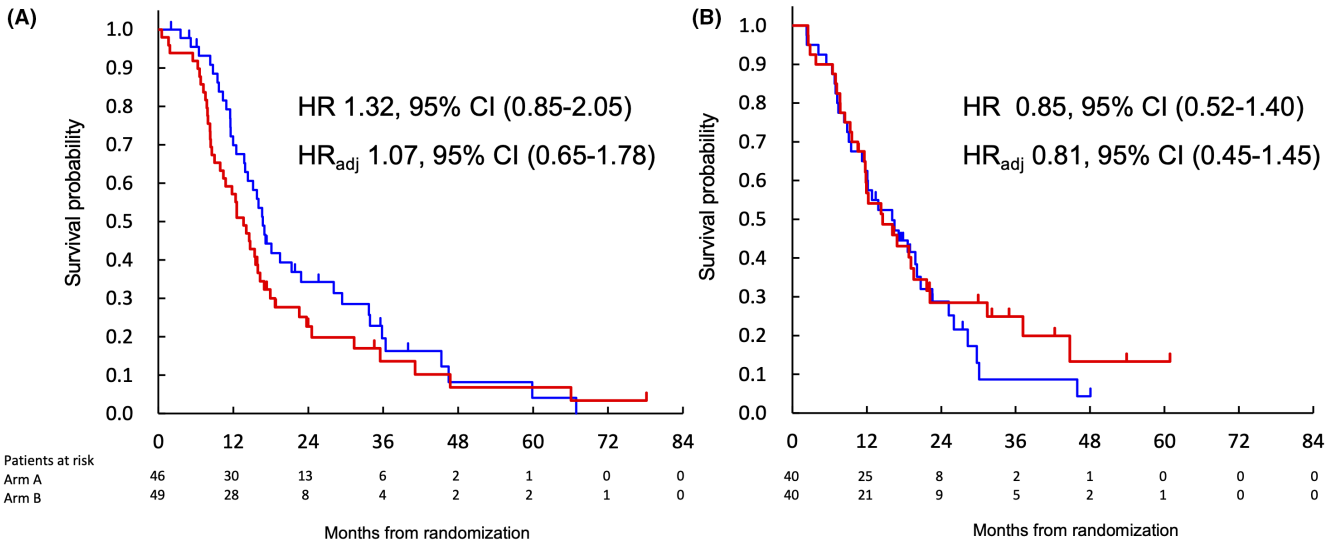

FIGURE 2 Overall survival according to countries. (A) Japanese patients ($n = 95$), (B) Korean patients ($n = 80$). The blue line represents the chemotherapy alone arm and the red line represents the gastrectomy + chemotherapy arm. Checkmarks represent censored patients. HR, hazard ratio. HRadj, adjusted hazard ratio, including the following variables as explanatory variables: country, age, sex, incurable factor, cT, cN, primary tumor location, performance status (PS), histological type, and macroscopic type.

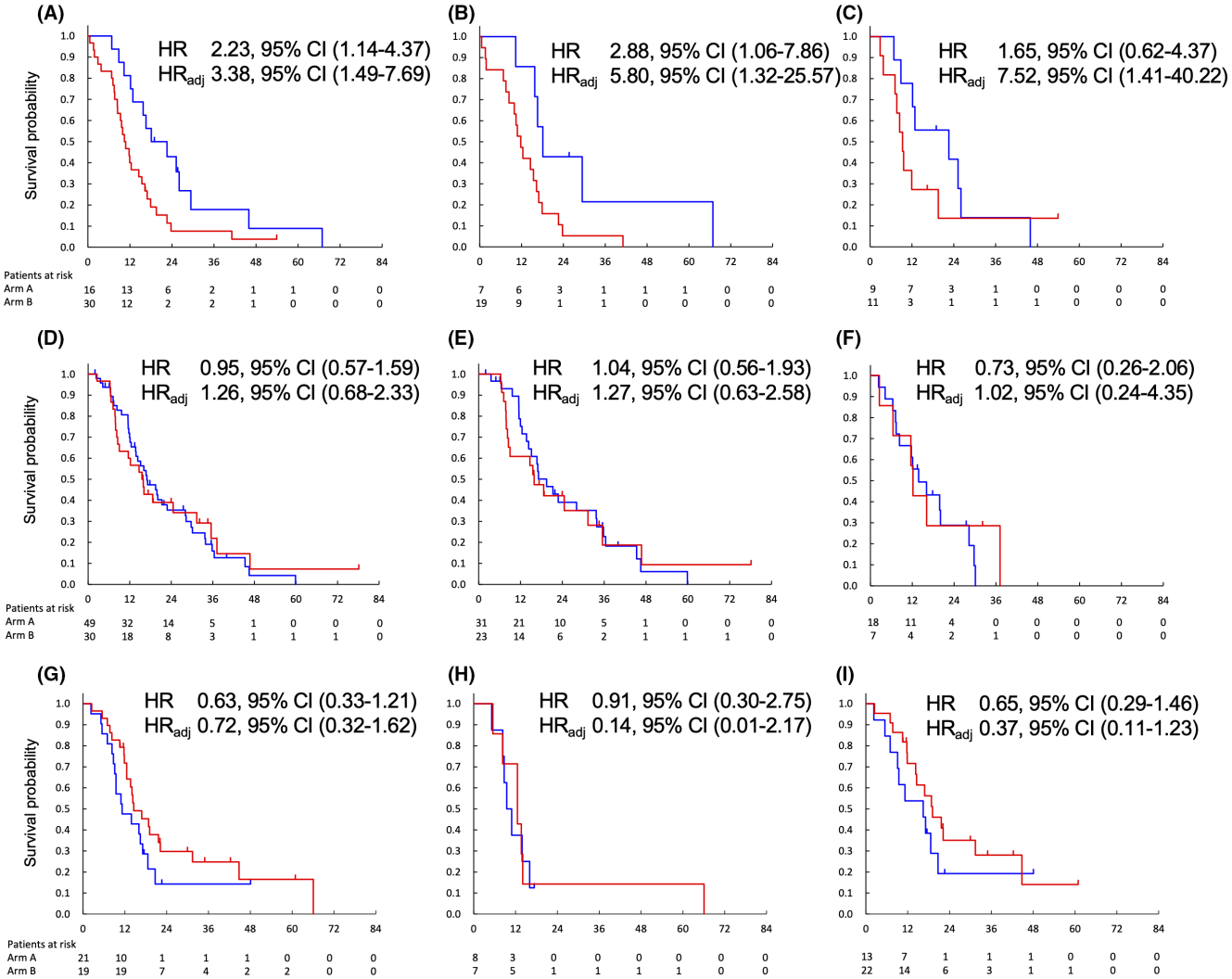

FIGURE 3 Overall survival according to countries and tumor location in all randomly assigned patients. The blue line represents the chemotherapy alone arm and the red line represents the gastrectomy + chemotherapy arm. Checkmarks represent censored patients. HR, hazard ratio. HRadj, adjusted hazard ratio, including the following variables as explanatory variables: country, age, sex, incurable factor, cT, cN, primary tumor location, performance status (PS), histological type, and macroscopic type. (A, B,) and (C) represent U-lesion; (D, E) and (F) represent M-lesion; and (G, H) and (I) represent L-lesion. (A, D,) and (G)in all patients; (B, E) and (H) in Japan; and (C, F) and (I) in Korea. The number of patients is 46, 26, 20, 79, 54, 25, 50, 15, and 35 in (A) to (I) respectively.

this supplementary analysis to explore the subgroups for which reduction gastrectomy might be beneficial according to country and tumor location. Hence, the results of reduction gastrectomy were worse in Japan than in Korea, although without a significant difference. In Korea, no difference was found in survival according to the presence or absence of gastrectomy. Rather, the survival was slightly better in the gastrectomy plus chemotherapy arm after 24 months. Furthermore, survival was worse in the gastrectomy plus chemotherapy arm than in the chemotherapy alone arm when this was analyzed by tumor location in U-lesion while no difference in M-lesion between the two arms in either country. The survival was slightly better in the gastrectomy plus chemotherapy arm than in the chemotherapy alone arm in the L-lesion, especially in Korea. This could be due to differences in various background factors, such as age in this cohort, although without significant difference in background factors in the general practice of gastric cancer between Japan and Korea.[6]

The most affecting factor was the number of chemotherapy treatment cycles. The number of chemotherapy cycles in the U-lesion did not differ much in Korea (6 vs. 5.5), whereas a large difference was observed in Japan (7 vs. 3). In contrast, a large difference was found in the number of treatment cycles in the L-lesion (3 vs. 6) in Korea, but not (4 vs. 4.5) in Japan. Additionally, the median number of chemotherapy cycles after gastrectomy was higher in Korea than in Japan, especially after distal gastrectomy (4 vs. 6.5). This may have contributed to better survival after distal gastrectomy in Korea.

The impact of second- or third-line treatment has been recently demonstrated, especially in Asian countries.[7] The proportion of patients who received second-line treatment seems lower in patients

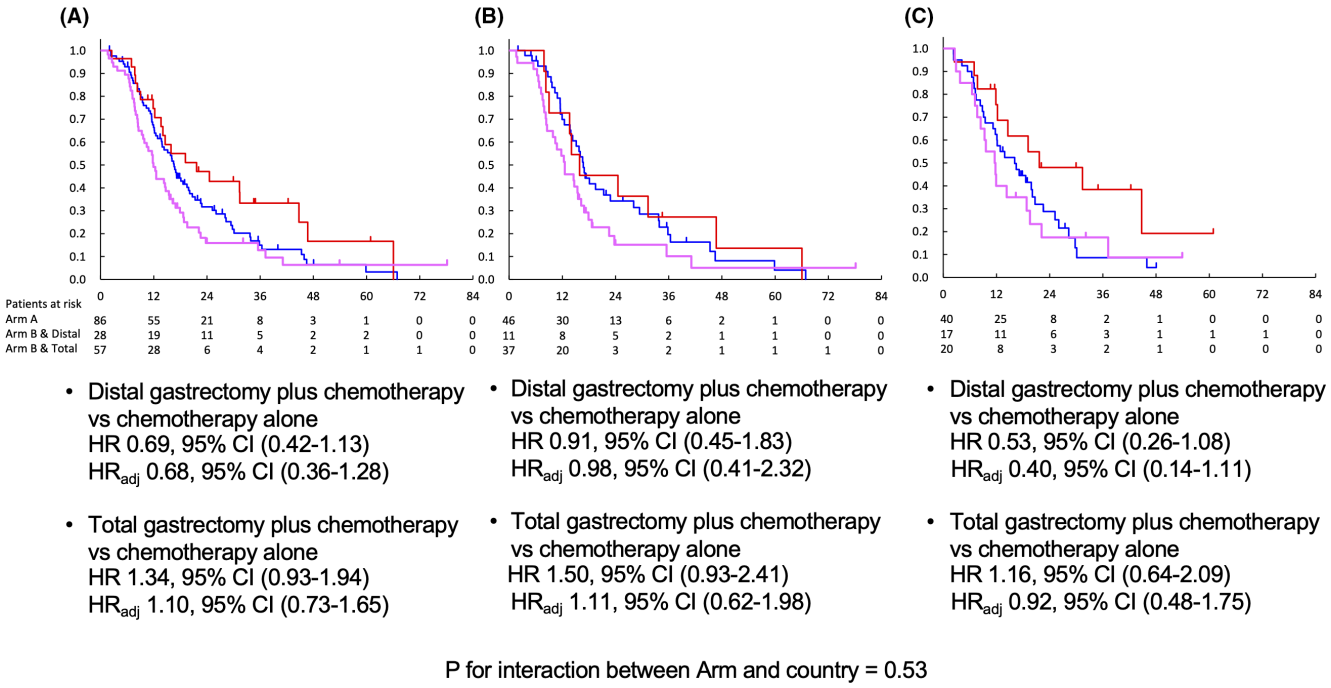

FIGURE 4 Overall survival according to countries and tumor location in all randomly assigned patients. The blue line represents the chemotherapy alone arm, the red line represents the distal gastrectomy + chemotherapy arm, and the pink line represents the total gastrectomy plus chemotherapy arm. Checkmarks represent censored patients. HR, hazard ratio. HRadj, adjusted hazard ratio, including the following variables as explanatory variables: country, age, sex, incurable factor, cT, cN, primary tumor location, performance status (PS), histological type, and macroscopic type. (A) represents all patients, (B) represents patients in Japan, and (C) represents patients in Korea.

with L-lesion and patients receiving distal gastrectomy in Korea. The second-line transition rates between the country and the treatment arm have heterogeneity, but it seems to have minimal impact on survival. Nevertheless, the duration of the first-line treatment appears to be important in this series.

Palliative gastrectomy is sometimes performed in patients with urgent symptoms. One of the factors that may have a significant impact on survival in patients undergoing palliative resection is the appropriate chemotherapy administration. The presence or absence of chemotherapy was recognized as a significant prognostic factor in a study of palliative resection in patients with urgent symptoms.[8] Furthermore, survival was better in patients receiving chemotherapy after palliative resection than in those without chemotherapy among patients with gastric outlet obstruction (GOO).[9] The present study revealed no difference in the number of treatment cycles in patients with L-lesions with or without surgery in Japan; however, it was twice as high in the group with surgery in Korea. The low number of treatment cycles in the chemotherapy alone arm in Korea is because many patients suffered from GOO after chemotherapy initiation although they did not have any symptoms at the time of enrollment.

Additionally, the survival in patients who underwent total gastrectomy was worse than that in patients with chemotherapy alone in both Japan and Korea in the comparison of the survival in chemotherapy alone arm and different resection type. Compliance was poorer after total gastrectomy than distal gastrectomy in postoperative adjuvant chemotherapy after radical gastrectomy.[10] Similar results were reported even in palliative resection.[11] The deterioration of nutritional status and general condition due to poor oral intake after total gastrectomy has a great influence on chemotherapy compliance. Care should be taken regarding the palliative resection indications, especially in cases requiring total gastrectomy. Conversely, regarding distal gastrectomy, no significant difference was found in survival between chemotherapy alone and surgery plus chemotherapy arms in Japan, while the surgery plus chemotherapy arm showed better survival than chemotherapy alone in Korea. This result was confirmed by multivariable Cox regression analysis. HRadj was different between Japan and Korea (0.98 vs. 0.40) due to the difference in treatment cycles after gastrectomy. Therefore, selecting a type of resection with a high possibility of continuing chemotherapy would be better in patients indicating distal gastrectomy depending on their condition.

So far, several meta-analyses of palliative resection were reported. Meta-analyses suggest the effectiveness of palliative resections; however, palliative resection increases postoperative complications.[12] The present study revealed that the enrolled patients were without subjective symptoms, such as GOO, at the time of enrollment. However, surgical procedures, such as bypass surgery, should also be considered for cases with some symptoms.

Additionally, the impact of palliative resection on patients for whom chemotherapy cannot be performed is unclear because chemotherapy is a major factor influencing survival. We have previously reported the effectiveness of palliative resection for patients who cannot receive chemotherapy.[13] This will be an issue for further study.

The present study had several limitations. First, the sample size was small, and statistically significant differences could not be detected. However, this is the only randomized controlled trial on reduction gastrectomy in the world, and the results may be valuable. Second, the dose intensity was not examined although the number of chemotherapy courses was given. The effect of gastrectomy on the dose intensity of chemotherapy is unknown. Third, the present study used the SP chemotherapeutic regimen. Immunotherapy has been recently introduced as the first-line chemotherapy for gastric cancer. Tumor response and patient survival have significantly improved compared with previous reports. Hence, the role of reduction surgery might be different when the chemotherapy regimen changes and should be reevaluated.

Primary chemotherapy is a standard of care for advanced gastric cancer with non-curable factors; however, the survival benefits from distal gastrectomy for reduction in tumors at the distal stomach remained controversial.

AUTHOR CONTRIBUTIONS

Concept and design: Kazumasa Fujitani, Toshimasa Tsujinaka, Kenichi Nakamura, Hiroshi Katayama, Han-Kwang Yang. Acquisition, analysis, or interpretation of data: Masanori Terashima, Kazumasa Fujitani, Hyuk-Joon Lee, Jun Ho Lee, Ji-Yeong An, Akinori Takagane, Young Kyu Park, Seung Ho Choi, Kyo Young Song, Seiji Ito, Do Joong Park, Sung-Ho Jin. Drafting of the manuscript: Masanori Terashima. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Junki Mizusawa. Supervision: Mitsuru Sasako.

CONFLICT OF INTEREST STATEMENT

Autor Junki Mizusawa received lecture fees from Taiho Pharmaceutical. Authior Narikazu Boku received lecture fee from Ono Pharmaceutical, Taiho Pharmaceutical, BMS, and grants from Ono pharmaceutical and Takeda pharmaceutical. Author Mitsuru Sasako received consulting fee from Ono Pharmaceutical and lecture fee from Taiho Pharmaceutical, Chugai Pharmaceutical, Ono Pharmaceutical, Sanofi. Author Hyuk-Joon Lee is a editorial bord member of *Annals of Gastroenterological Surgery*. The other authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

Individual participant data that support the results after de-identification will be shared with investigators whose proposed use of the data has been approved by the investigators from the JCOG Stomach Cancer Study Group. Proposals should be directed to m.terashima@scchr.jp.

ETHICS STATEMENT

Approval of the research protocol: All procedures followed were under the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964 and later versions.

Informed consent: Written informed consent, including permission for the secondary use of the trial data, was obtained from all patients upon enrollment in JCOG0705/KGCA01. UMIN-CTR, number UMIN000001012.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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