Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial

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Summary

Background Chemotherapy is the standard of care for incurable advanced gastric cancer. Whether the addition of gastrectomy to chemotherapy improves survival for patients with advanced gastric cancer with a single non-curable factor remains controversial. We aimed to investigate the superiority of gastrectomy followed by chemotherapy versus chemotherapy alone with respect to overall survival in these patients.

Methods We did an open-label, randomised, phase 3 trial at 44 centres or hospitals in Japan, South Korea, and Singapore. Patients aged 20–75 years with advanced gastric cancer with a single non-curable factor confined to either the liver (H1), peritoneum (P1), or para-aortic lymph nodes (16a1/b2) were randomly assigned (1:1) in each country to chemotherapy alone or gastrectomy followed by chemotherapy by a minimisation method with biased-coin assignment to balance the groups according to institution, clinical nodal status, and non-curable factor. Patients, treating physicians, and individuals who assessed outcomes and analysed data were not masked to treatment assignment. Chemotherapy consisted of oral S-1 80 mg/m² per day on days 1–21 and cisplatin 60 mg/m² on day 8 of every 5-week cycle. Gastrectomy was restricted to D1 lymphadenectomy without any resection of metastatic lesions. The primary endpoint was overall survival, analysed by intention to treat. This study is registered with UMIN-CTR, number UMIN000001012.

Findings Between Feb 4, 2008, and Sept 17, 2013, 175 patients were randomly assigned to chemotherapy alone (86 patients) or gastrectomy followed by chemotherapy (89 patients). After the first interim analysis on Sept 14, 2013, the predictive probability of overall survival being significantly higher in the gastrectomy plus chemotherapy group than in the chemotherapy alone group at the final analysis was only 13·2%, so the study was closed on the basis of futility. Overall survival at 2 years for all randomly assigned patients was 31·7% (95% CI 21·7–42·2) for patients assigned to chemotherapy alone compared with 25·1% (16·2–34·9) for those assigned to gastrectomy plus chemotherapy. Median overall survival was 16·6 months (95% CI 13·7–19·8) for patients assigned to chemotherapy alone and 14·3 months (11·8–16·3) for those assigned to gastrectomy plus chemotherapy (hazard ratio 1·09, 95% CI 0·78–1·52; one-sided p=0·70). The incidence of the following grade 3 or 4 chemotherapy-associated adverse events was higher in patients assigned to gastrectomy plus chemotherapy than in those assigned to chemotherapy alone: leucopenia (14 patients [18%] *vs* two [3%]), anorexia (22 [29%] *vs* nine [12%]), nausea (11 [15%] *vs* four [5%]), and hyponatraemia (seven [9%] *vs* four [5%]). One treatment-related death occurred in a patient assigned to chemotherapy alone (sudden cardiopulmonary arrest of unknown cause during the second cycle of chemotherapy) and one occurred in a patient assigned to chemotherapy plus gastrectomy (rapid growth of peritoneal metastasis after discharge 12 days after surgery).

Interpretation Since gastrectomy followed by chemotherapy did not show any survival benefit compared with chemotherapy alone in advanced gastric cancer with a single non-curable factor, gastrectomy cannot be justified for treatment of patients with these tumours.

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Introduction

The prognosis of patients with advanced gastric cancer with non-curable factors, such as hepatic, peritoneal, or distant lymph node metastases, is poor—most patients die within 1 year. Chemotherapy is the standard of care for these patients. For incurable advanced gastric cancer, palliative resection or bypass surgery is generally indicated in the presence of major symptoms such as bleeding or obstruction, whereas the usefulness of gastrectomy aimed at reduction of tumour volume (ie, reductive gastrectomy) in asymptomatic patients is still unclear. Findings from studies from the early 1980s to early 2000s[1–9] suggested that the addition of gastrectomy to chemotherapy, even in the absence of any serious symptoms such as bleeding and obstruction, might improve patient survival (median overall survival

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed, Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials databases without language restrictions for studies published between Jan 1, 1985, and Dec 31, 2014, using the terms "gastric cancer", "non-curative OR advanced", "gastrectomy OR surgery", "chemotherapy", and "randomized". We also searched clinical trial registers (ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform) for ongoing randomised trials. The final search was done on April 30, 2015. Although in the past 30 years there has been much interest in the safety and efficacy of gastrectomy in patients with non-curative gastric cancer, most studies were retrospective case series involving selected patients, spanning a wide timeframe, and with variable methods and reporting, and none was randomised. We identified only one relevant ongoing randomised trial comparing gastrectomy plus metastasectomy followed by systemic therapy versus systemic therapy alone in advanced gastric cancer.

Added value of this study

To our knowledge, REGATTA is the first randomised controlled trial to address the survival benefit of reduction surgery before chemotherapy as first-line treatment of advanced gastric cancer. We recruited patients with a single non-curable factor since this population was the most likely to obtain a survival benefit from a surgically reduced tumour burden. Patients were randomly assigned to receive either D1 gastrectomy plus chemotherapy or chemotherapy alone with S-1 plus cisplatin as first-line treatment. Findings from this study showed that primary surgery before chemotherapy does not yield any survival benefit and is not recommended in the clinical management of incurable gastric cancer.

Implications of all the available evidence

To our knowledge, this study provides the first high-quality evidence for reduction surgery before chemotherapy in patients with non-curative gastric cancer. Patients with incurable gastric cancer should undergo upfront chemotherapy. Our findings could change the practice of reduction surgery for non-curative gastric cancer and are applicable to a broad population of patients with advanced gastric cancer worldwide.

of 8·0–12·2 months with gastrectomy *vs* 2·4–6·7 months without gastrectomy) among patients with advanced gastric cancer with a single non-curable factor. However, most of these studies were retrospective, single institutional case series, and were confounded by substantial selection bias because patients with good Eastern Cooperative Oncology Group (ECOG) performance status, fewer comorbidities, and small tumour burden were more likely to undergo gastrectomy, thereby resulting in a positive outcome. Furthermore, in the past decade, a median overall survival of about 12 months has been reported with chemotherapy alone,[10–14] making the role of additional gastrectomy in the treatment of non-curable advanced gastric cancer unclear.

Theoretically, gastrectomy might reduce a large and potentially immunosuppressive tumour burden, remove the source of new metastases, and ameliorate symptoms caused by the gastric lesion, thereby facilitating durable systemic chemotherapy. By contrast, gastrectomy could enhance the growth of metastatic lesions by inducing immunosuppression, delay the start of systemic chemotherapy because of postoperative complications, increase toxicity, and decrease tolerability of chemotherapy. In the past decade, findings from several clinical studies of first-line chemotherapy for metastatic or recurrent gastric cancer[15–18] have shown that past gastrectomy along with a small number of metastatic sites are independent favourable prognostic factors, which suggest the relevance of reducing tumour burden for achieving longer overall survival in patients with advanced gastric cancer.

To the best of our knowledge, no randomised controlled trial has investigated whether additional gastrectomy confers a survival benefit over chemotherapy alone in patients with non-curable advanced gastric cancer.[19] Here, we report the final results of a multi-institutional, randomised, controlled trial (REGATTA) that was done to establish whether the addition of gastrectomy to standard chemotherapy improves survival among patients with advanced gastric cancer with a single non-curable factor.

Methods

Study design and participants

REGATTA was an open-label, randomised, phase 3 trial done by the Japan Clinical Oncology Group (JCOG; JCOG0705) and the Korean Gastric Cancer Association (KGCA; KGCA01). Patients aged 20–75 years with histologically proven primary gastric adenocarcinoma and presence of a single non-curable factor confirmed by both enhanced abdominal CT and exploratory laparoscopy or laparotomy were eligible. A single non-curable factor was defined as hepatic metastasis (H1; two to four lesions of maximum diameter ≤5 cm and minimum diameter ≥1 cm); peritoneal metastasis (P1) in the diaphragm or peritoneum caudal to the transverse colon without massive ascites or intestinal obstruction; or para-aortic lymph node metastasis above the coeliac axis or below the inferior mesenteric artery (lymph node 16a1/b2 of maximum diameter ≥1 cm), or both. Para-aortic lymph node (16a1/b2) metastasis does not include metastatic nodes located inside the anatomical landmarks of a possible D3 extended lymphadenectomy, which

corresponds to the para-aortic nodal stations located below the coeliac axis and above the inferior mesenteric artery. Inclusion criteria were clinical T1–3 disease diagnosed via staging laparoscopy or laparotomy; no distant metastasis other than H1, P1, or lymph node 16a1/b2; no apparent pleural effusion; oesophageal invasion of 3 cm or smaller without any need for resection by a thoracotomy; ECOG performance status of 0 or 1; sufficient oral intake without active bleeding from the gastric tumour; no previous chemotherapy or radiation therapy for any other malignancies and no previous treatment for gastric cancer except endoscopic submucosal dissection; and adequate organ function, defined as a leucocyte count of $3 \cdot 0$–$12 \cdot 0 \times 10^9$ cells per L, haemoglobin concentration at least 80 g/L without any transfusion within the 2 weeks before enrolment, platelet count at least 100×10^9 cells per L, aspartate or alanine aminotransferase concentration 100 IU/L or lower, total bilirubin concentration $34 \cdot 2$ μmol/L or lower, serum creatinine $106 \cdot 1$ μmol/L or lower, and creatinine clearance at least 60 mL/min. Tumours were staged in accordance with the Japanese Classification of Gastric Carcinoma.[20] Exploratory laparoscopy or laparotomy was mandatory to assure the presence of a single non-curable factor since peritoneal metastasis is sometimes accompanied by other non-curable factors, such as liver metastasis.

Patients were excluded if they had any of the following criteria: active coexisting cancer (synchronous coexisting cancer and metachronous cancer within 5 disease-free years) to ensure complete exclusion of the previous cancer effect on overall survival excluding carcinoma in situ (lesions equivalent to intraepithelial or intramucosal cancer); pregnant or breastfeeding; a severe mental disorder; systemic administration of corticosteroids; flucytosine, phenytoin, or warfarin treatment; active bacterial infection or mycosis with systemic effects; unstable angina or myocardial infarction within 6 months before enrolment; unstable hypertension; diabetes mellitus, uncontrolled or controlled with insulin; and severe respiratory disease requiring continuous oxygen treatment. Additionally, patients with HER2-positive advanced gastric cancer were excluded since trastuzumab in combination with chemotherapy has become the standard treatment for these patients.[13]

The study protocol was approved by the JCOG protocol review committee and the institutional review board of each participating hospital before initiation of the study. This study was done in accordance with 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 enrolment.

Randomisation and masking

Eligible patients were registered at Japanese institutions by telephone or fax to the JCOG Data Centre, and via a web-based system with the Seoul National University Hospital (SNUH) Data Centre at institutions in South Korea and Singapore. Patients were randomly assigned (1:1) to gastrectomy followed by chemotherapy or chemotherapy alone in each country by a minimisation method with biased-coin assignment to balance the groups on the basis of institution, clinical nodal status (N0–1 *vs* N2–3), and non-curable factor (hepatic, peritoneal *vs* para-aortic metastasis). Patients and all investigators were unmasked to treatment assignment.

Each data centre did central monitoring to ensure data submission, patient eligibility, protocol compliance, safety, and on-schedule study progress. Monitoring reports were reviewed and issued by each data centre independently, with masking of survival data for each group. Monitoring reports were exchanged between the two data centres.

Procedures

In patients assigned to gastrectomy followed by chemotherapy, a total, distal, or proximal gastrectomy with D1 lymph node dissection was done depending on tumour location. Except for perigastric lymph node metastases, the metastatic lesions remained untouched. Neither complete D2 lymphadenectomy nor combined resection of adjacent organs except for the gallbladder, mesocolon, and diaphragm was acceptable. Laparoscopic gastrectomy or thoracotomy was not allowed. Within 8 weeks of surgery, the patient was placed on a chemotherapy regimen of S-1 plus cisplatin, which is a standard treatment for advanced gastric cancer in east Asia.[10]

All patients received oral S-1 80 mg/m² per day (80–120 mg/day total dose depending on the patient's body surface area as follows: <$1 \cdot 25$ m², 80 mg; $1 \cdot 25$–$1 \cdot 5$ m², 100 mg; and >$1 \cdot 5$ m², 120 mg) on days 1–21 of every 5-week cycle and cisplatin 60 mg/m² on day 8 of every 5-week cycle. We delayed every treatment cycle until non-haematological toxic effects had recovered to grade 1 or had resolved, body temperature was 38°C or lower, neutrophil count was at least $1 \cdot 5 \times 10^9$ cells per L, haemoglobin concentration was at least 80 g/L, platelet count was at least 75×10^9 cells per L, aspartate aminotransferase and alanine aminotransferase concentrations were 100 IU/L or lower, total bilirubin was $34 \cdot 2$ μmol/L or lower, and creatinine concentration was $106 \cdot 1$ μmol/L or lower. We reduced the treatment dose if, during the previous cycle, one of the following events had occurred: grade 3 or 4 neutropenia (<$1 \cdot 0 \times 10^9$ cells per L); thrombocytopenia (<50×10^9 cells per L); aspartate or alanine aminotransferase concentrations greater than 150 IU/L; total bilirubin greater than $51 \cdot 3$ μmol/L; creatinine concentration greater than $132 \cdot 6$ μmol/L; or grade 3 or worse non-haematological toxic effects. We discontinued treatment if disease progression was diagnosed clinically or by imaging, if a serious adverse event arose, if a treatment cycle was delayed owing to an adverse event continuing for longer than 3 weeks, if an adverse event meant a subsequent dose reduction was needed after the

second reduction, if the patient refused treatment, or if judged necessary by the attending physician for other reasons.

In patients assigned to chemotherapy alone, palliative gastrectomy was allowed only when severe uncontrollable symptoms such as bleeding and obstruction emerged during chemotherapy. Additionally, gastrectomy with curative intent could be done if deemed possible because complete disappearance of all non-curable factors identified upon registration was noted on CT. In the case of P1 disease, exploratory laparoscopy or laparotomy was mandatory before surgical intervention to assure curability.

Outcomes

The primary endpoint was overall survival, defined as the time from random assignment to death from any cause or to the last date of contact for a surviving patient. Secondary endpoints were progression-free survival, defined as the time from random assignment to the first occurrence of disease progression, death from any cause, or the latest date at which progression-free status was verified; and safety, defined as adverse events associated with either gastrectomy or chemotherapy.

Both gastrectomy-related and chemotherapy-related complications were assessed according to the Common Terminology Criteria for Adverse Events (version 3.0). Patients were assessed at least monthly from baseline for adverse events via verbal interview, physical examination, and blood tests, including a complete blood cell count and assessments of liver and renal function, until disease progression. Abdominal CT and measurements of carcinoembryonic antigen and carbohydrate antigen 19-9 were done every 3 months.

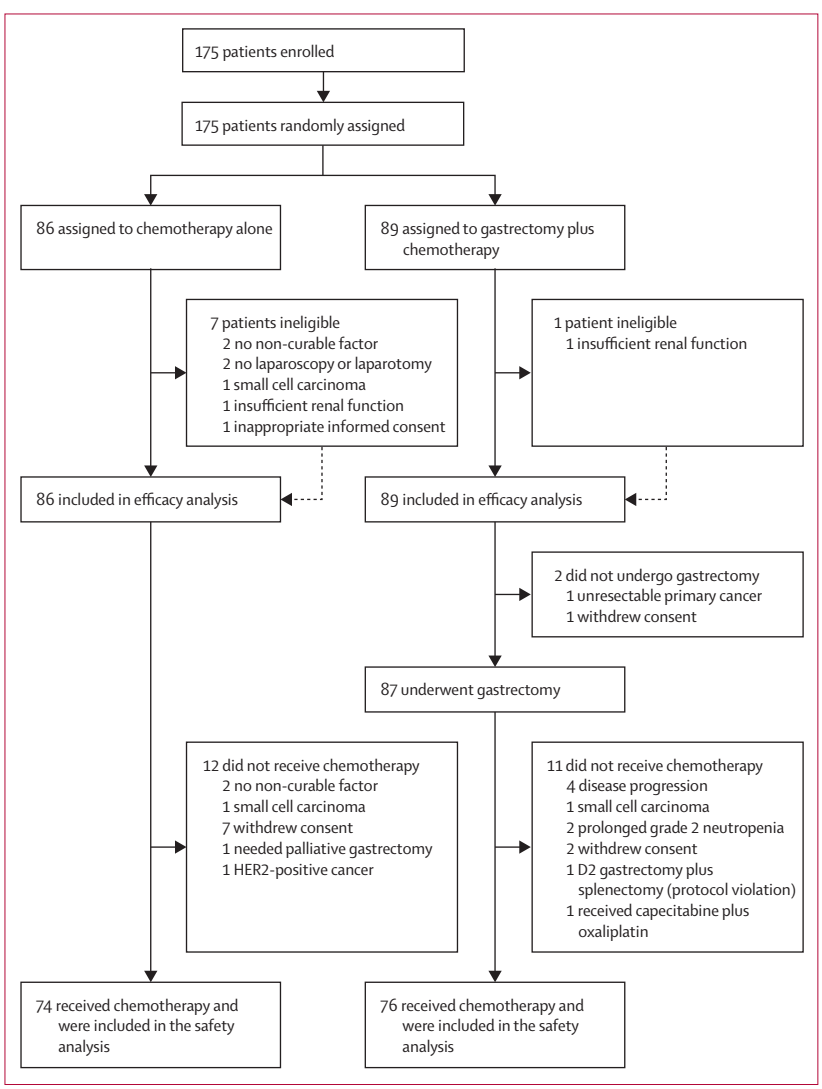

Figure 1: **Trial profile**

Statistical analysis

This study was designed to assess the superiority of gastrectomy followed by chemotherapy compared with chemotherapy alone in terms of overall survival. The planned sample size needed for 294 deaths to have occurred by the primary analysis was 330 (165 per group), with a one-sided α of 5% and 80% statistical power to detect a 2-year survival difference of 10% (20% with chemotherapy alone *vs* 30% with gastrectomy plus chemotherapy). 2 years of follow-up were planned after 4 years of patient accrual. Because of slow patient accrual, the protocol was amended on May 22, 2012, to prolong the total accrual period from 4 years to 5·5 years with 2 years of follow-up.

Two interim analyses were planned, with adjustments for repeated comparisons taken into account with the Lan and DeMets method and the O'Brien-Fleming type α spending function.[21,22] The first interim analysis was planned for the date at which half of the planned sample size had been enrolled, and the second interim analysis was planned for when the entire planned sample size had been enrolled. The prespecified stopping criteria in the study protocol were as follows: if survival for gastrectomy plus chemotherapy was superior to that of chemotherapy alone with a p value less than the adjusted significance level of 0·001354, study termination owing to efficacy would be considered, but if the survival curve for gastrectomy plus chemotherapy was below that for chemotherapy alone (ie, hazard ratio [HR] >1·0), study termination owing to futility would be considered, taking account of various factors such as toxicity profile in both groups and information time at the interim analysis (ie, the ratio of reported events at the interim analysis to the expected number of events at the final analysis). The data and safety monitoring committee of the JCOG independently reviewed the interim analysis report and could decide to stop the study early, with the agreement of the SNUH Data Centre.

Data from all randomised patients were analysed for overall survival and progression-free survival on an intention-to-treat basis. We estimated survival curves

using the Kaplan-Meier method and compared them using the stratified log-rank test with country as a stratum. HRs were estimated using a stratified Cox regression model with country as a stratum. We also did preplanned (by country) and post-hoc (other variables besides country) subgroup analyses to assess interactions between treatment and subgroup in Cox regression models. Safety was assessed on a per-protocol basis. The p value for the primary analysis of overall survival is one sided; all other p values are two sided. Statistical analyses were done by the JCOG Data Centre and confirmed by the SNUH Data Centre. Analyses were done with SAS software, version 9.2.

This study is registered with UMIN-CTR, number UMIN000001012.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study after termination of the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 4, 2008, and Sept 17, 2013, 175 patients (95 in Japan and 80 in South Korea) were enrolled and randomly assigned to chemotherapy alone (86 patients) or gastrectomy plus chemotherapy (89 patients; figure 1) at 44 cancer centres, medical centres, university hospitals, and general hospitals in Japan, South Korea, and Singapore. Seven patients in the chemotherapy alone group were ineligible, as was one patient in the gastrectomy plus chemotherapy group. Two patients assigned to gastrectomy plus chemotherapy did not undergo gastrectomy (figure 1). Defined chemotherapy was not delivered in 23 patients: 12 in the chemotherapy alone group and 11 in the gastrectomy plus chemotherapy group (figure 1). Of the 175 randomly assigned patients, the 25 who did not receive study treatment after random assignment were excluded from the safety population (12 in the chemotherapy alone group and 13 in the gastrectomy plus chemotherapy group).

Table 1 shows patient demographics, tumour characteristics, and surgical procedures. Both groups were well balanced except for primary tumour location, which was equally distributed in patients assigned to gastrectomy plus chemotherapy, but more than half of the patients assigned to chemotherapy alone had middle-third tumours. The most frequent non-curable factor was peritoneal metastasis in 131 (75%) of 175 patients; the distribution of non-curable factors was similar in both groups.

The first interim analysis was done on Sept 14, 2013, for the 164 enrolled patients based on data as of June 3, 2013. The JCOG Data and Safety Monitoring Committee recommended early termination of the study according to the prespecified stopping criteria on the basis of futility, with 110 (37%) of the expected 294 events reported, because the predictive probability of overall survival being significantly higher in the gastrectomy plus chemotherapy group than in the chemotherapy alone group would be 13·2% at the final analysis even if accrual continued to the planned number. Overall survival at 2 years was 25·7% (95% CI 15·7–36·9) for gastrectomy followed by chemotherapy and 31·4% (20·4–42·9) for chemotherapy alone (HR 1·08, 95% CI 0·74–1·58; one-sided p=0·66 by the stratified log-rank test).

	Chemotherapy alone (n=86)	Gastrectomy plus chemotherapy (n=89)
Age (years)	59 (49–67)	62 (54–66)
Country		
Japan	46 (53%)	49 (55%)
South Korea	40 (47%)	40 (45%)
Sex		
Male	56 (65%)	61 (69%)
Female	30 (35%)	28 (31%)
Non-curable factor		
Liver metastasis (H1)	5 (6%)	11 (12%)
Peritoneal metastasis (P1)	66 (77%)	65 (73%)
Para-aortic lymph node metastasis (16a1/b2)	11 (13%)	13 (15%)
Missing	4 (5%)*	0
Location of primary tumour		
Upper third	16 (19%)	30 (34%)
Middle third	49 (57%)	30 (34%)
Lower third	21 (24%)	29 (33%)
Clinical tumour stage		
T2	8 (9%)	9 (10%)
T3	78 (91%)	80 (90%)
Clinical nodal stage		
N0–1	47 (55%)	45 (51%)
N2–3	39 (45%)	44 (49%)
Histological type†		
Intestinal	21 (24%)	22 (25%)
Diffuse	65 (76%)	67 (75%)
Macroscopic type		
0–3 or 5	61 (71%)	65 (73%)
4	25 (29%)	24 (27%)
Surgical procedure		
Proximal gastrectomy	..	2 (2%)
Distal gastrectomy	..	28 (31%)
Total gastrectomy	..	57 (64%)
Exploratory laparotomy	..	1 (1%)
Missing	..	1 (1%)‡

Data are median (IQR) or number (%). Some percentages do not add up to 100 because of rounding. *Two patients without a non-curable factor and two patients who did not undergo laparoscopy or laparotomy. †Based on the Lauren classification. ‡Withdrew informed consent.

Table 1: **Demographics and baseline characteristics**

Between June 3, 2013, when 164 patients had been enrolled, and Sept 17, 2013, when patient accrual was stopped, another 11 patients were recruited, resulting in the final enrolment of 175 patients. In an updated analysis on Dec 1, 2014, with a median follow-up of 14·5 months (range 0·5–78·2) for all randomly assigned patients, 71 (83%) of 86 patients assigned to chemotherapy alone and 73 (82%) of 89 assigned to gastrectomy plus chemotherapy had died. There were 144 events reported in 175 enrolled patients, which was 49% (144/294) of the expected events.

Overall survival at 2 years for all randomly assigned patients was 31·7% (95% CI 21·7–42·2) for patients assigned to chemotherapy alone compared with 25·1% (16·2–34·9) for those assigned to gastrectomy plus chemotherapy. Median overall survival was 16·6 months (95% CI 13·7–19·8) for patients assigned to chemotherapy alone and 14·3 months (11·8–16·3) for those assigned to gastrectomy plus chemotherapy (HR 1·09, 95% CI 0·78–1·52; one-sided p=0·70, by the stratified log-rank test; figure 2). We calculated similar findings in a per-protocol analysis that excluded eight patients judged as ineligible and 25 patients who did not receive planned chemotherapy (HR 1·01, 95% CI 0·71–1·44).

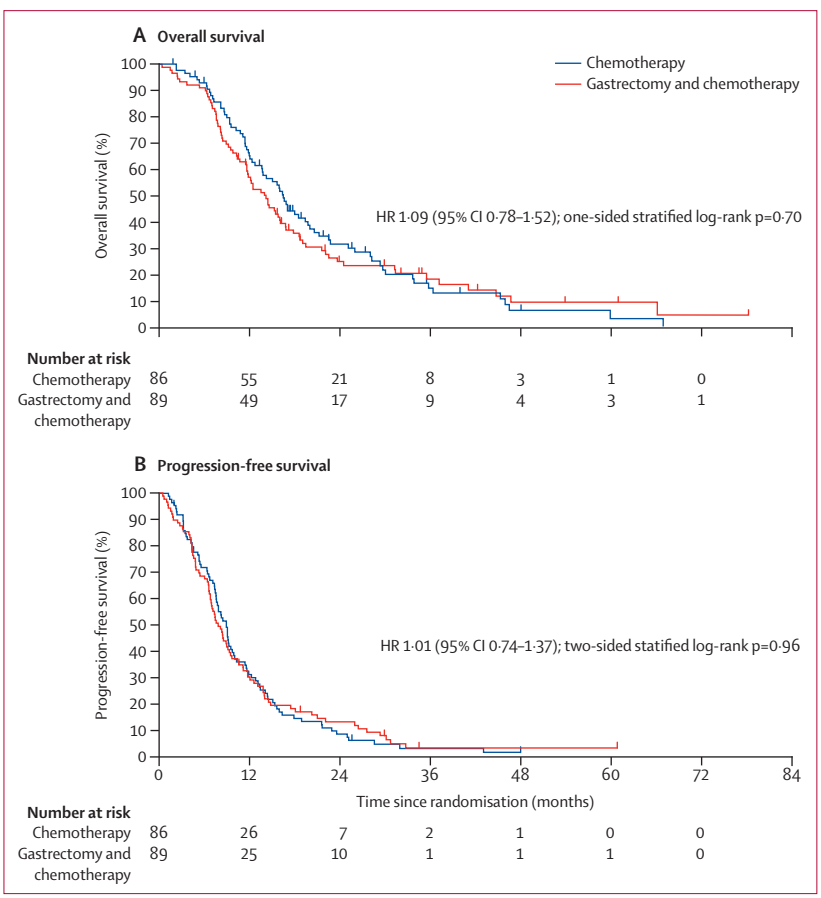

Figure 2: **Overall survival and progression-free survival in all randomly assigned patients**
Checkmarks represent censored patients. HR=hazard ratio.

82 (95%) of 86 patients assigned to chemotherapy alone and 83 (93%) of 89 assigned to gastrectomy plus chemotherapy had disease progression. 2-year progression-free survival was 8·4% (95% CI 3·7–15·5) for patients assigned to chemotherapy alone and 13·0% (6·9–21·2) for those assigned to gastrectomy plus chemotherapy (HR 1·01, 95% CI 0·74–1·37; two-sided p=0·96; figure 2). Among the 86 patients assigned to chemotherapy alone, five underwent gastrectomy with curative intent because of complete disappearance of all non-curable factors during chemotherapy. At the time of the updated analysis, three were alive but had signs of recurrence, one was free of disease progression, and one had died.

In prespecified subgroup analysis by country, and exploratory subgroup analyses for other subgroups, of overall survival, we noted significant interactions between treatment effect and both clinical N stage and tumour location (figure 3). The effect of gastrectomy plus chemotherapy compared with chemotherapy alone on overall survival was significantly unfavourable 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 tumours (2·23, 1·14–4·37; two-sided p=0·017).

Table 2 shows the number of cycles of chemotherapy actually delivered by tumour location. The median number of chemotherapy cycles was 7·0 (IQR 6–9) in patients with N0–1 disease who were assigned to chemotherapy alone and 4·5 (3–6) in those assigned to gastrectomy plus chemotherapy. In patients with upper-third tumours who had gastrectomy, all of whom underwent total gastrectomy, the median number of chemotherapy cycles was reduced after gastrectomy to half of that for chemotherapy alone. By contrast, compliance with chemotherapy was well maintained even after gastrectomy in patients with lower-third tumours, of whom 20 (69%) of 29 underwent distal gastrectomy.

Mean relative dose intensities of S-1 and cisplatin for the planned doses during the first three courses of chemotherapy were 93% (SD 18) and 97% (5), respectively, in patients assigned to chemotherapy alone, and 84% (19) and 94% (8), respectively, in those assigned to gastrectomy plus chemotherapy.

Median duration of surgery was 180 min (IQR 140–210), with a median blood loss of 200 mL (100–398) among patients assigned to gastrectomy plus chemotherapy. Grade 2 or worse adverse events occurred in 14 (16%) of the 87 patients who underwent gastrectomy. The incidence of six major surgery-related complications of grade 3 or worse were pancreatic fistula in one patient (1%), intra-abdominal abscess in one patient (1%), wound infection in two patients (2%), postoperative bleeding in one patient (1%), anastomotic leakage in no patients, and pneumonia in no patients. Ileus occurred in two patients and pleural effusion in one patient, but these were minor complications. No patient underwent reoperation.

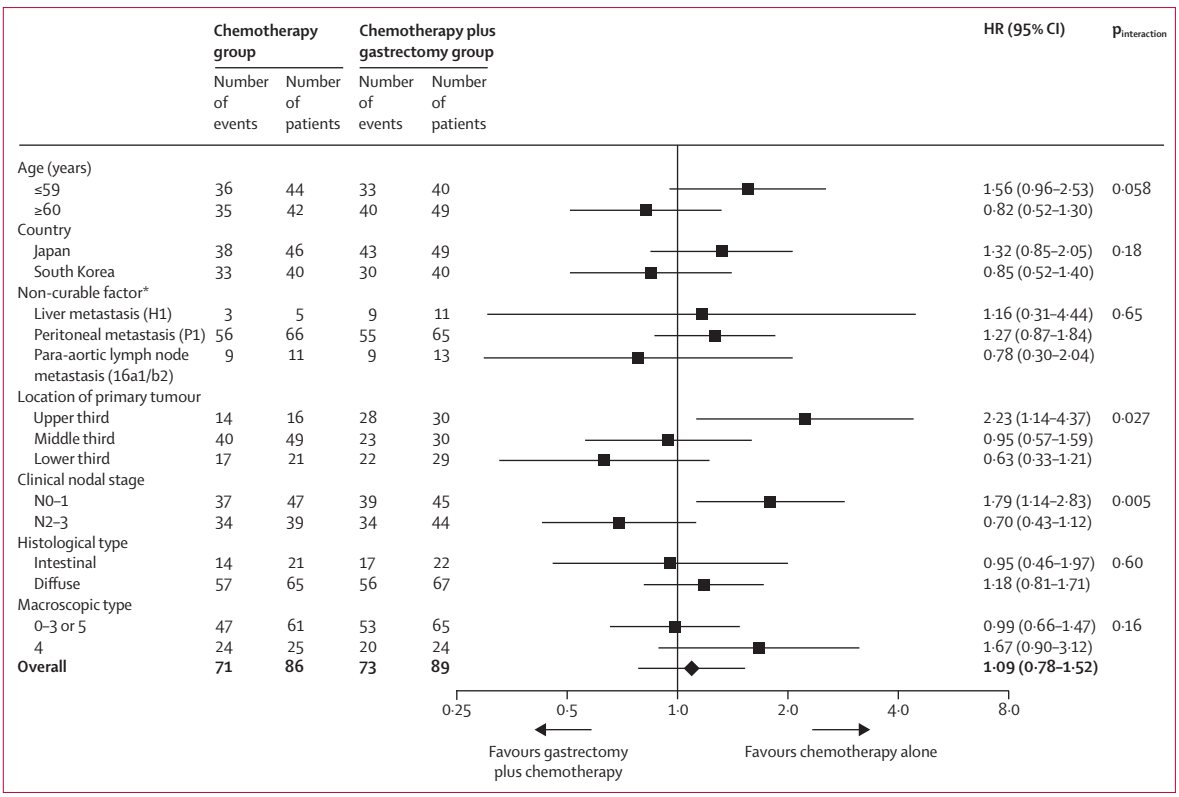

Figure 3: **Subgroup analyses**
HRs for death in the patients assigned to gastrectomy plus chemotherapy are shown with 95% CIs. HR=hazard ratio. *Data missing for four patients in the chemotherapy alone group.

Hospital death, defined as death during the hospital stay for gastrectomy or death from any cause within 30 days after surgery, occurred in one patient (1%), due to aggressive progression of unresectable primary tumour just after exploratory laparotomy. Additionally, gastrectomy with curative intent was safely done without any postoperative complications, with a median operative time of 267 min (IQR 211–291) and median blood loss of 415 mL (381–510) in the five patients initially assigned to chemotherapy alone. Neither thrombosis nor pulmonary embolism occurred during the protocol treatment, including during the postoperative state in both groups.

Table 3 shows adverse events associated with chemotherapy. The incidence of grade 3 or worse leucopenia, anorexia, nausea, and hyponatraemia was higher in patients assigned to gastrectomy plus chemotherapy than in those assigned to chemotherapy alone. One treatment-related death was reported in a patient assigned to chemotherapy alone (sudden cardiopulmonary arrest of unknown cause during the second cycle of chemotherapy) and one occurred in a patient assigned to chemotherapy plus gastrectomy (rapid growth of peritoneal metastasis after discharge 12 days after surgery). The median time to commencing chemotherapy after gastrectomy was 31 days (range 16–57). Chemotherapy was discontinued in 21 (28%) of 74 patients assigned to chemotherapy alone and 27 (36%) of 76 patients assigned to gastrectomy plus chemotherapy.

	Chemotherapy		Gastrectomy plus chemotherapy	
	Number of patients	Median number of cycles (IQR)	Number of patients	Median number of cycles (IQR)
Tumour location				
Upper third*	16	6 (4–8)	30	3 (2–5)
Middle third†	49	6 (5–8)	30	5 (4–8)
Lower third‡	21	4 (2–6)	29	6 (3–8)
Total	74	6 (3–8)	76	5 (3–7)

*Ten patients were not treated with chemotherapy. †Seven patients were not treated with chemotherapy. ‡Eight patients were not treated with chemotherapy.

Table 2: **Number of chemotherapy cycles delivered by tumour location**

Discussion

In this study, gastrectomy plus chemotherapy did not provide a survival advantage compared with chemotherapy alone in the treatment of advanced gastric cancer with a single non-curable factor. The study was terminated after the interim analysis because patients assigned to gastrectomy plus chemotherapy were unlikely to have improved overall survival compared

	Chemotherapy alone (n=74)			Gastrectomy plus chemotherapy (n=76)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Leucopenia	43 (58%)	1 (1%)	1 (1%)	48 (63%)	9 (12%)	5 (7%)
Neutropenia	30 (41%)	21 (28%)	3 (4%)	32 (42%)	22 (29%)	10 (13%)
Anaemia	55 (74%)	10 (14%)	6 (8%)	56 (74%)	15 (20%)	4 (5%)
Thrombocytopenia	41 (55%)	4 (5%)	1 (1%)	46 (61%)	4 (5%)	3 (4%)
Febrile neutropenia*	0	4 (5%)	0	0	4 (5%)	0
Anorexia*	36 (49%)	9 (12%)	0	32 (43%)	22 (29%)	0
Nausea*	37 (50%)	4 (5%)	0	30 (40%)	11 (15%)	0
Fatigue*	38 (51%)	5 (7%)	0	40 (53%)	4 (5%)	0
Vomiting*	17 (23%)	2 (3%)	0	18 (24%)	4 (5%)	0
Diarrhoea*	16 (22%)	5 (7%)	0	34 (45%)	2 (3%)	0
Stomatitis*	15 (20%)	2 (3%)	0	13 (17%)	2 (3%)	0
Hand-foot syndrome*	11 (15%)	0	0	11 (15%)	0	0
Increased creatinine	19 (26%)	0	0	24 (32%)	0	0
Hyponatraemia	40 (54%)	4 (5%)	0	34 (45%)	7 (9%)	0
Sensory neuropathy†	8 (26%)	0	0	2 (7%)	1 (3%)	0

Data are number (%). Severity was graded according to the Common Terminology Criteria for Adverse Events (version 3.0). According to the data and safety monitoring committee, one patient in each group died from an adverse event related to treatment. *Data missing for one patient in the gastrectomy plus chemotherapy group. †Data were collected only in Japan after about a third of patients were enrolled (chemotherapy alone, n=31; gastrectomy plus chemotherapy, n=30).

Table 3: **Haematological and non-haematological adverse events associated with chemotherapy**

with those assigned to chemotherapy alone. 2-year overall survival did not differ between patients assigned to chemotherapy alone and those assigned to gastrectomy plus chemotherapy.

In this study, we did not need to prove that gastrectomy plus chemotherapy was worse than chemotherapy alone, since, in view of the more invasive nature of additional gastrectomy, it should be better as a standard treatment. Our study was terminated before the planned sample size was accrued, which meant that we had limited power to detect a difference between groups. Had the trial reached full accrual, the predictive probability of gastrectomy plus chemotherapy having a significantly better overall survival than chemotherapy alone would have been 13·2% on the basis of the Bayesian approach by Spiegelhalter and colleagues.[23]

In post-hoc subgroup analyses of overall survival, there was a significant interaction between treatment effect and tumour location. Gastrectomy plus chemotherapy was associated with significantly worse overall survival in patients with upper-third tumours. In patients with upper-third tumours, the median number of chemotherapy cycles was reduced after gastrectomy to half of that for chemotherapy alone. We believe that this impaired compliance with chemotherapy after gastrectomy accounted for the worse overall survival than with chemotherapy alone. By contrast, compliance with chemotherapy was similar between groups in patients with lower-third tumours, resulting in comparable overall survival. Compliance with chemotherapy after gastrectomy is inversely associated with the amount of postoperative bodyweight loss, which is generally more evident after total gastrectomy than after any other types of gastrectomy.[24] When considering the substantial increase in the incidence of gastro-oesophageal junction cancer in high-income countries, which requires a total gastrectomy for cure, the reduced compliance with chemotherapy after total gastrectomy reported here would have a worldwide effect on treatment strategy. Additionally, this worse chemotherapy compliance after gastrectomy is universal, as shown in the MAGIC trial[25] in which a perioperative regimen of epirubicin, cisplatin, and fluorouracil was administered to European patients with advanced gastric cancer, with chemotherapy compliance of 86% preoperatively and 76% postoperatively. Therefore, we believe that the results of this trial are applicable to a broad population of patients with advanced gastric cancer worldwide. Postoperative complications are less likely to cause lower compliance with chemotherapy because of the low incidence of surgical morbidity and mortality in this study.

In a post-hoc analysis, we also noted a significant interaction between treatment effect and clinical N stage. Gastrectomy plus chemotherapy was associated with worse overall survival in patients with N0–1. Since the median number of chemotherapy cycles was higher in patients with N0–1 disease who were assigned to chemotherapy alone than in those assigned to gastrectomy plus chemotherapy, decreased compliance with chemotherapy also accounted for worse overall survival. The higher proportion of upper-third tumours in patients in the gastrectomy plus chemotherapy group could explain this decreased compliance with chemotherapy.

Primary tumour location was not balanced between groups. This imbalance might have had an effect on the negative finding of this trial since significant interaction was noted between treatment effect and primary tumour location. If inclusion criteria were restricted to the patients with lower-third tumour, findings from this study might have been positive, although patient accrual would have been more difficult.

Whether removal of the primary tumour from patients with metastatic disease confers a survival benefit is gaining increased attention. Regarding metastatic renal cell carcinoma, findings from two randomised trials[26,27] have shown that nephrectomy followed by interferon significantly improves overall survival compared with interferon alone. In a population-based cohort study of patients with incurable stage IV colorectal cancer,[28] palliative primary tumour resection was associated with improved overall and cancer-specific survival compared with no resection. In patients with colon cancer with unresectable metastases, a multicentre randomised controlled trial comparing primary tumour resection with no resection before systemic chemotherapy is underway to assess the survival benefit of primary tumour resection,[29] and other ongoing randomised phase 3 trials are assessing the role of primary surgery in

metastatic colon (NCT02363049) and rectal cancer (NCT02314182). In patients with non-curable metastatic gastric cancer, another randomised trial is ongoing—the GYMSSA trial[30]—in which gastrectomy plus metastasectomy followed by systemic treatment is being compared with systemic therapy alone in terms of overall survival and adverse events, with a planned enrolment of 136 patients. Since one group in that trial involves removal of the metastatic tumours as well, the aim of the study is different from the present study, which focused on pure reduction surgery without metastasectomy.

In this study, five patients initially assigned to chemotherapy alone underwent gastrectomy with curative intent because of complete disappearance of all non-curable factors during chemotherapy. This finding raises the question as to whether a new trial should be done to investigate the effect of conversion surgery, in which each patient is given upfront chemotherapy and is randomly assigned in the case of achieving a systemic control to gastrectomy or continuing chemotherapy. Although the value of conversion surgery must be investigated in a randomised trial, conversion surgery could be a possible treatment option since no survival benefit of upfront gastrectomy was shown in this trial. However, patient recruitment would be much more difficult for a new trial examining conversion surgery than it was for this trial.

The present study has some limitations. First, the planned sample size was not achieved because early termination was recommended by the JCOG Data and Safety Monitoring Committee on the basis of the overall futile effect and ethical reasons, restricting the statistical power to support conclusions. Second, the quality of the study was partly impaired because eight (5%) patients were judged as ineligible and 25 (14%) did not receive planned chemotherapy, which might have affected outcomes, although the HR for death was essentially unchanged in patients assigned to gastrectomy plus chemotherapy when calculated in a per-protocol analysis. Third, assessment of quality of life was not done, which is a crucial consideration for patients with a limited lifespan when choosing the optimum treatment strategy. Finally, no nutritional parameters were collected, despite their importance in gastric cancer, especially in metastatic presentation.

Although the study investigators were masked to efficacy data for each treatment at the interim analysis, only data and safety monitoring committee members and an independent statistician who was not in charge of this study were able to review the unmasked safety and efficacy data at the interim analysis because of the asymmetrical risk balance between two groups due to the more invasive nature of gastrectomy plus chemotherapy than chemotherapy alone.

This study had many intrinsic difficulties in patient accrual in view of its strict eligibility criteria, patient preferences, and biases of individual clinicians, which led to poor acceptance of random assignment. Although a complete screening log is not available, our case survey of the first 241 eligible patients showed that 82 (34%) patients were successfully enrolled, 98 (41%) declined enrolment, and 61 (25%) did not receive any explanation of this study. Of the 159 patients who did not enter this study, 104 (65%) were treated with chemotherapy alone. Despite these difficulties with enrolment, we were able to finish this study and obtain clear conclusions.

To the best of our knowledge, this is the first randomised controlled trial to show no survival benefit of additional gastrectomy over chemotherapy alone in patients with non-curable advanced gastric cancer. In conclusion, gastrectomy plus chemotherapy cannot be justified to treat patients with advanced gastric cancer, even with a single non-curable factor. Chemotherapy alone remains the standard of care for these patients.

Contributors

MS had the original idea. KF wrote the protocol, assisted by KN, YK, MS, and TT. H-KY and TT chaired the study group and were co-primary investigators. DJP and YK were involved in creating international collaborations. All authors except JM, SH, KN, and BJP recruited patients into the study. JM, SH, KN, and BJP were responsible for data management, statistical analysis, and interpretation. KF and TT wrote the report, with revisions from all the other authors.

Declaration of interests

TY, YK, and MS have received lecture fees from Taiho Pharmaceutical. Y-JB has received grant support from Taiho Pharmaceutical. MS has received grant support and lecture fees from Taiho Pharmaceutical. TT has received grant support from the Ministry of Health, Labour and Welfare of Japan, and lecture fees from Taiho Pharmaceutical. All other authors declare no competing interests.

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