Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial

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Summary

Background D2 gastrectomy is recommended in US and European guidelines, and is preferred in east Asia, for patients with resectable gastric cancer. Adjuvant chemotherapy improves patient outcomes after surgery, but the benefits after a D2 resection have not been extensively investigated in large-scale trials. We investigated the effect on disease-free survival of adjuvant chemotherapy with capecitabine plus oxaliplatin after D2 gastrectomy compared with D2 gastrectomy only in patients with stage II–IIIB gastric cancer.

Methods The capecitabine and oxaliplatin adjuvant study in stomach cancer (CLASSIC) study was an open-label, parallel-group, phase 3, randomised controlled trial undertaken in 37 centres in South Korea, China, and Taiwan. Patients with stage II–IIIB gastric cancer who had had curative D2 gastrectomy were randomly assigned to receive adjuvant chemotherapy of eight 3-week cycles of oral capecitabine (1000 mg/m² twice daily on days 1 to 14 of each cycle) plus intravenous oxaliplatin (130 mg/m² on day 1 of each cycle) for 6 months or surgery only. Block randomisation was done by a central interactive computerised system, stratified by country and disease stage. Patients, and investigators giving interventions, assessing outcomes, and analysing data were not masked. The primary endpoint was 3 year disease-free survival, analysed by intention to treat. This study reports a prespecified interim efficacy analysis, after which the trial was stopped after a recommendation by the data monitoring committee. The trial is registered at ClinicalTrials.gov (NCT00411229).

Findings 1035 patients were randomised (520 to receive chemotherapy and surgery, 515 surgery only). Median follow-up was 34·2 months (25·4–41·7) in the chemotherapy and surgery group and 34·3 months (25·6–41·9) in the surgery only group. 3 year disease-free survival was 74% (95% CI 69–79) in the chemotherapy and surgery group and 59% (53–64) in the surgery only group (hazard ratio 0·56, 95% CI 0·44–0·72; p<0·0001). Grade 3 or 4 adverse events were reported in 279 of 496 patients (56%) in the chemotherapy and surgery group and in 30 of 478 patients (6%) in the surgery only group. The most common adverse events in the intervention group were nausea (n=326), neutropenia (n=300), and decreased appetite (n=294).

Interpretation Adjuvant capecitabine plus oxaliplatin treatment after curative D2 gastrectomy should be considered as a treatment option for patients with operable gastric cancer.

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Introduction

Gastric cancer is the second most common cause of cancer-related mortality worldwide, with 988 000 new cases and 736 000 deaths per year.[1] Surgery is the main treatment for operable gastric cancer; however, recurrence rates are high (about 40–80% in advanced cases).[2,3] In east Asia, particularly in Japan and South Korea, D2 gastrectomy is the standard surgical treatment for localised gastric cancer.[4,5] In Europe, two randomised controlled studies done in the UK[6] and the Netherlands[7] showed little initial difference between D1 and D2 surgery. However, long-term follow-up of the Dutch trial showed a reduction in gastric cancer-specific deaths with extended surgery,[8] a finding that has been supported by findings from a smaller Taiwanese study.[9] As a result of these findings, D2 gastrectomy is now recommended in European[10] and US treatment guidelines[11] for resectable disease.

Adjuvant chemotherapy is a standard component of resectable gastric cancer therapy and improves patient outcomes,[12,13] although the preferred treatment differs by geographical region. The recommended adjuvant treatment is chemoradiotherapy in the USA,[11] perioperative chemotherapy in the UK and parts of Europe,[10] and adjuvant chemotherapy in Japan.[4] These recommendations are based on the US Intergroup-0116[14] and UK Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC)[15] trials, which showed survival benefits with postoperative chemoradiotherapy and perioperative chemotherapy, respectively, compared with surgery alone. However, the benefits were evident only after limited dissection of regional lymph nodes in both studies, raising questions about the need for postoperative radiotherapy or perioperative chemotherapy after D2 gastrectomy.[16,17] The Japanese recommendation for

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adjuvant therapy is based on the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) study,[13,18] which showed a survival benefit with adjuvant chemotherapy after D2 gastrectomy compared with surgery alone. A subgroup analysis of the data showed a survival benefit for stages II and IIIA disease.

Increased acceptance of D2 gastrectomy raises new questions about the optimum adjuvant therapy for patients with operable gastric cancer. The Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) study was designed to compare the effect of adjuvant capecitabine plus oxaliplatin after D2 gastrectomy with surgery alone on disease-free survival in patients with stage II or III gastric cancer. Although several phase 2 trials have shown the activity of capecitabine and oxaliplatin in advanced gastric cancer,[19–22] phase 3 data for this regimen in gastric cancer are absent. We summarise the results of the prespecified interim analysis from the CLASSIC study, which was done after a recommendation by the independent data monitoring committee to fully assess and report the study.

Methods

Study design and patients

CLASSIC was a randomised, open-label, multicentre, parallel-group, phase 3 study. The trial was done in 37 centres in South Korea, China, and Taiwan.

Eligible patients were ambulatory; aged 18 years or older; had histologically confirmed, American Joint Committee on Cancer/Union Internationale Contre le Cancer[23] stage II (T2N1, T1N2, T3N0), IIIA (T3N1, T2N2, T4N0), or IIIB (T3N2) gastric adenocarcinoma with no evidence of metastatic disease; and had had D2 surgery and achieved R0 resection. Patients were included only if they had a Karnofsky performance status of 70% or more. Patients who had had chemotherapy, immunotherapy, or radiotherapy for gastric cancer were excluded. Patients had to have adequate renal function (creatinine clearance >50 mL/min or serum creatinine ≤1·5 times the upper limit of normal [ULN]), hepatic function (total bilirubin ≤1·5 times the ULN, aspartate or alanine aminotransferase ≤2·5 times the ULN, alkaline phosphatase ≤2·5 times the ULN), and haematological function (absolute neutrophil count ≥1·5×10⁹/L or platelet count ≥100×10⁹/L).

The protocol was approved by the institutional review board at each participating institution, and the study was done in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines defined by the International Conference on Harmonization. All patients provided written, informed consent.

See Online for webappendix

Randomisation and masking

Patients were randomly assigned to receive capecitabine and oxaliplatin or surgery alone in a 1:1 ratio. Randomisation was done after surgery with a centralised interactive computerised system and stratified by country and disease stage (II, IIIA, and IIIB). A random permuted block design (with a block size of four) was used in each combination of country and stage of disease stratum. Because study centre was not a stratification factor, a particular study centre could not predict the next allocation, or even know how many numbers in the block had already being allocated if they had correctly guessed the block size. Patients, and investigators giving interventions, assessing outcomes, and analysing data were not masked.

Procedures

All patients had curative D2 gastrectomy within 6 weeks before randomisation. At least 15 lymph nodes were examined to ensure adequate disease classification. All surgeons had experience doing this type of surgery (>50 procedures per year). To further ensure the quality of surgery, standard operating procedures were predefined and given to all surgeons before the start of the study, and surgery was photographed.

Patients assigned to the chemotherapy group received eight 3-week cycles of oral capecitabine (1000 mg/m² twice daily on days 1–14 of each cycle) plus intravenous oxaliplatin (130 mg/m² on day 1 of each cycle). Dose reductions or interruptions were allowed to manage potentially serious or life-threatening adverse events. Subsequent dose escalations for capecitabine were allowed after two more cycles in the absence of grade 2–4 toxic effects, if oxaliplatin was permanently discontinued. For toxic effects judged to be due to only one drug, the dose of the other drug was not modified. In cases of oxaliplatin-related neurological adverse events, capecitabine could be continued as monotherapy. Oxaliplatin monotherapy was not allowed if capecitabine was discontinued.

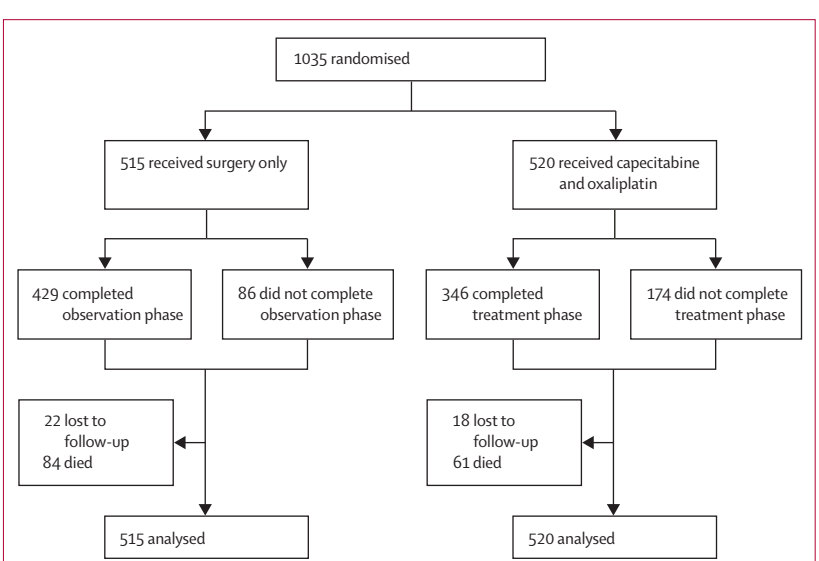


Figure 1: **Trial profile**
Numbers of patients eligible not available. Reasons for withdrawal during the study treatment or observation phase are given in the webappendix.

Prespecified tumour assessments to assess whether patients were disease free were done by abdominal CT or MRI every 6 months during the first 3 years and yearly thereafter, and by chest radiograph every 3 months for the first 2 years, every 6 months for the subsequent year, and yearly thereafter. If signs or symptoms indicated a possible recurrence or development of a new gastric cancer, investigations were then done to verify whether the patient was disease free. The same assessment was used for each patient.

Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0). Adverse events were documented during chemotherapy and for 28 days after the last dose of study medication. In the surgery only group, adverse events were recorded for up to 190 days after randomisation. Relative dose intensity was defined as the dose received divided by the planned dose for the eight treatment cycles.

The primary endpoint was 3 year disease-free survival, defined as the time from randomisation to the time of recurrence of the original gastric cancer, development of a new gastric cancer, or death from any cause. Secondary endpoints were overall survival (defined as the time from the date of randomisation to date of death from any cause) and safety (any adverse event).

Statistical analysis

3 year disease-free survival in the oxaliplatin and capecitabine and surgery only groups was predicted to be 65·0% and 56·2%, respectively (hazard ratio [HR] 0·75, with the assumption of a 3 year dropout rate of 10% with recruitment for 12 months). The null hypothesis (no difference in 3 year disease-free survival between study groups) was tested with Cox proportional hazards regression stratified by country and disease stage, with covariates of age, sex, and nodal metastatic status. A sample size of 512 patients in each group was planned to record 385 disease-free survival events with 80% power at a 0·05 significance level by a two-sided log-rank test.

An interim efficacy analysis was scheduled for after 257 events (66·8% of the number of events at final analysis), with stopping boundaries decided by application of the Lan-DeMets method[24] and O'Brien-Fleming α spending function[25] using the actual number of events. Interim efficacy analyses for disease-free survival and overall survival were done with Cox proportional hazards regression by intention to treat. All efficacy analyses were repeated per protocol to test the sensitivity of the results (data not shown). Safety was assessed per protocol.

Time to event endpoints were analysed with Kaplan-Meier survival methods. Estimates of treatment effect were calculated as HRs with 95% CIs. Study treatment groups were compared with a two-sided log-rank test. We also did a prespecified analysis of disease-free survival in subgroups.

This Article reports a planned interim analysis of data, which was triggered because the necessary number of events had occurred. The trial was then stopped after a recommendation by the independent data monitoring committee, who reviewed the data in March, 2011.

The trial was registered at ClinicalTrials.gov (NCT00411229).

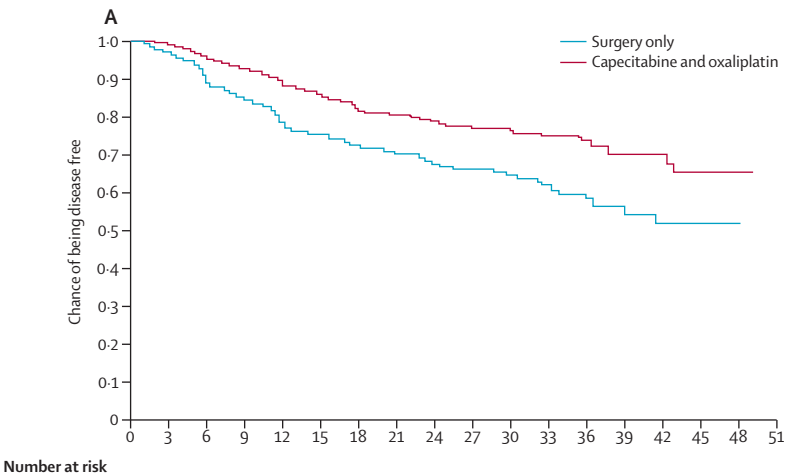
Role of the funding source

The study sponsor helped to design the study, to interpret data, and helped with the decision to submit the report for publication in conjunction with the authors. Employees of the sponsor collected, managed, and analysed data. The sponsors funded writing assistance. The two principal investigators (Y-JB and SHN) had full access to all study data and had final responsibility for the decision to submit for publication.

	Surgery only (n=515)	Capecitabine and oxaliplatin (n=520)
Age (years)	55·8 (11·6)	56·1 (11·1)
Men	358 (70%)	373 (72%)
Karnofsky performance status (%)	90% (90–100)	90% (90–100)
Body surface area (m^2)	1·62 (0·15)	1·62 (0·15)
Time since surgery (months)	1·14 (0·17)	1·14 (0·17)
AJCC/UICC[23] stage		
IB	0 (0%)	1 (<1%)
II	261 (51%)	253 (49%)
IIIA	184 (36%)	193 (37%)
IIIB	69 (13%)	73 (14%)
IV	1 (<1%)	0 (0%)
Tumour stage		
T1	3 (1%)	8 (2%)
T2	282 (55%)	282 (54%)
T3	229 (44%)	227 (44%)
T4	1 (<1%)	3 (1%)
Tumour location*		
Antrum	234 (45%)	237 (46%)
Body	172 (33%)	166 (32%)
Body and antrum	29 (6%)	31 (6%)
Fundus	40 (8%)	46 (9%)
Fundus and body	13 (3%)	10 (2%)
Gastro-oesophageal junction	9 (2%)	15 (3%)
Whole gastric	6 (1%)	6 (1%)
Other†	12 (2%)	9 (2%)
Lymph nodes examined	43·6 (16·7)	45·0 (17·4)
Nodal status		
N0	56 (11%)	47 (9%)
N1	308 (60%)	313 (60%)
N2	151 (29%)	160 (31%)

Data are mean (SD), n (%), or median (IQR). Intention-to-treat population; all patients were Asian. AJCC/UICC=American Joint Cancer Committee/Union Internationale Contre le Cancer. *Antrum is the lower third, body the middle third, and fundus the upper third. †Includes multiple localisations.

Table 1: **Baseline patient characteristics**



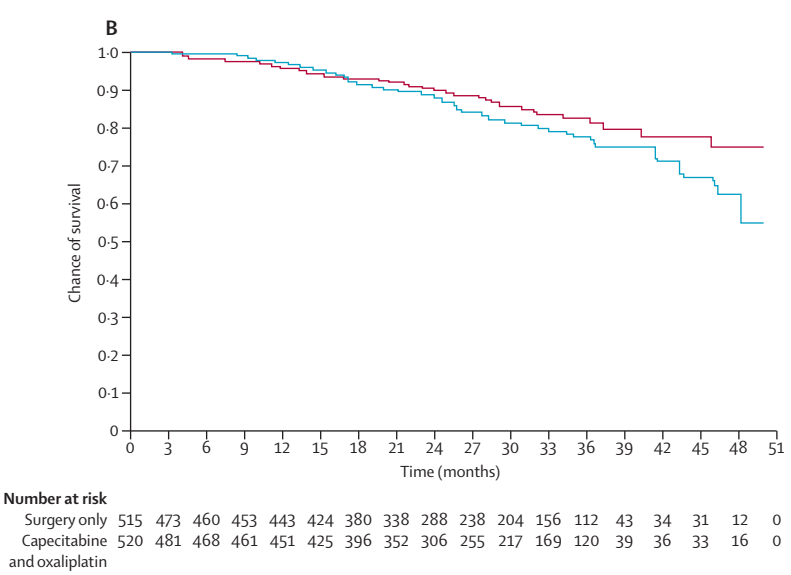


Figure 2: **3 year disease-free survival (A) and preliminary overall survival (B) in the intention-to-treat population**

Results

Figure 1 shows the trial profile. Between June, 2006, and June, 2009, 1035 patients were randomly assigned to receive either oxaliplatin and capecitabine (n=520) or surgery only (n=515; intention-to-treat population). The trial was stopped because accrual was complete and the necessary 257 disease-free survival events had occurred. The median duration of follow-up was 34·2 months (25·4–41·7) in the chemotherapy group and 34·3 months (25·6–41·9) in the surgery only group; 468 patients were followed up in the chemotherapy group and 463 in the surgery only group. Patient demographic and baseline disease characteristics were similar in each group (table 1).

At the cutoff for the interim analysis, 106 patients (20%) in the chemotherapy group had relapsed, developed a new gastric cancer, or died, compared with 163 patients (32%) in the surgery only group. 3 year disease-free survival was higher in the chemotherapy group than in the surgery only group (HR 0·56, 95% CI 0·44–0·72; p<0·0001). 3 year disease-free survival was 74% (95% CI 69–79) in the chemotherapy group and 59% (53–64) in the surgery only group. Kaplan-Meier curves for disease-free survival show early separation between the two study groups (figure 2A).

65 patients (13%) died in the chemotherapy group compared with 85 (17%) in the surgery only group. 3 year overall survival was 83% (95% CI 79–87) in the chemotherapy group and 78% (74–83) in the surgery only group (HR 0·72, 95% CI 0·52–1·00; p=0·0493; figure 2B), although a robust estimate of median overall survival is not yet available.

In the chemotherapy group, 96 patients (18%) developed recurrences or new occurrences of gastric cancer compared with 155 patients (30%) in the surgery only group. The sites of gastric cancer recurrence or new occurrence were the peritoneum (47 in the chemotherapy group *vs* 56 in the surgery only group), locoregional sites (21 *vs* 44), and distant sites (49 *vs* 78).

Subgroup analysis of 3-year disease-free survival showed consistent benefit for oxaliplatin and capecitabine compared with surgery only for several factors (figure 3). Survival was significantly higher in the chemotherapy group than in the surgery only group for all disease stages (figure 3). 3 year disease-free survival for stage II disease was 85% (95% CI 79–90) for chemotherapy and 71% (64–78) for surgery alone, for stage IIIa disease 66% (57–75) for chemotherapy and 51% (42–60) for surgery alone, and for stage IIIb disease 61% (48–73) for chemotherapy and 33% (95% CI 15%–51%) for surgery alone.

For nodal status 1 and 2 subgroups 3 year disease-free survival was significantly improved with oxaliplatin and capecitabine compared with surgery only, but not for nodal status 0 (figure 3).

Of the 1035 randomised patients, 61 were excluded from the safety population (25 in the chemotherapy group *vs* 36 in the surgery only group). The main reasons for exclusion were absence of follow-up information (18 *vs* 36) and not receiving study treatment after randomisation (22 in the chemotherapy group). Additionally, one patient in the surgery only group received chemotherapy in error, and was included in the chemotherapy group for the safety analysis. The safety population included 496 patients in the chemotherapy group and 478 patients in the surgery only group.

346 patients (67%) assigned to the chemotherapy group received eight cycles as planned. 167 patients had capecitabine dose reductions, 147 had cycle interruptions, and 369 had cycle delays, and 163 patients needed oxaliplatin dose reductions. The median relative dose intensity was 85% for capecitabine and 98% for oxaliplatin.

Table 2 shows adverse events reported by 10% or more of patients. Almost nine times as many grade 3 or

4 adverse events were reported in the chemotherapy group than in the surgery group. The most commonly reported adverse events at any grade in the chemotherapy group were nausea, neutropenia, decreased appetite, peripheral neuropathy, diarrhoea, and vomiting (table 2). The most common grade 3 or 4 adverse events in the chemotherapy group were neutropenia, thrombocytopenia, nausea, and vomiting (table 2). Grade 3 or 4 peripheral neuropathy, a cumulative toxic effect associated with oxaliplatin, occurred in 12 (2%) patients. 43 patients (9%) had serious adverse events related to chemotherapy. Two patients died within 28 days of the last dose of treatment in the chemotherapy group: one because of sepsis (possibly related to treatment), and one because of metastatic gastric cancer (judged unrelated to the study treatment). One patient in the surgery only group died because of cardiac failure during the observation phase.

Adverse events led to chemotherapy dose modifications in 446 (90%) patients; neutropenia, nausea, vomiting, thrombocytopenia, and decreased appetite were the most common reasons (webappendix). Discontinuations because of adverse events in the chemotherapy group occurred in 50 (10%) patients, mainly as a result of neutropenia (n=17; 3%), thrombocytopenia (n=5; 1%), and vomiting (n=5; 1%).

Discussion

This study shows that a 6 month course of chemotherapy after D2 gastrectomy improves 3 year disease-free survival compared with surgery only. Chemotherapy reduced the relative risk of disease recurrence, new disease occurrence, or death compared with surgery alone. Moreover, a subgroup analysis suggested that adjuvant capecitabine and oxaliplatin was beneficial for all disease stages (II, IIIA or IIIB). The overall survival data from our study are not yet mature; however, the data suggest an improvement in overall survival with capecitabine and oxaliplatin compared with surgery only. An analysis after a median follow-up of 5 years is planned to conclusively establish the overall survival benefit of capecitabine and oxaliplatin in this setting.

We used 3 year disease-free survival as the primary endpoint because most relapses occur within 3 years of surgery.[26] Although 3 year disease-free survival has not yet been formally validated as a surrogate measure, preliminary data from the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group indicate that 3 year disease-free survival is strongly correlated with 5 year overall survival, the benchmark for judging effectiveness of adjuvant therapy in gastric cancer.[27] The clinical relevance of disease-free survival in gastric cancer is supported by the GASTRIC group meta-analysis of 17 trials, which showed an 18% relative risk reduction for both disease-free survival and overall survival with adjuvant chemotherapy compared with surgery only in patients with resectable disease.[12]

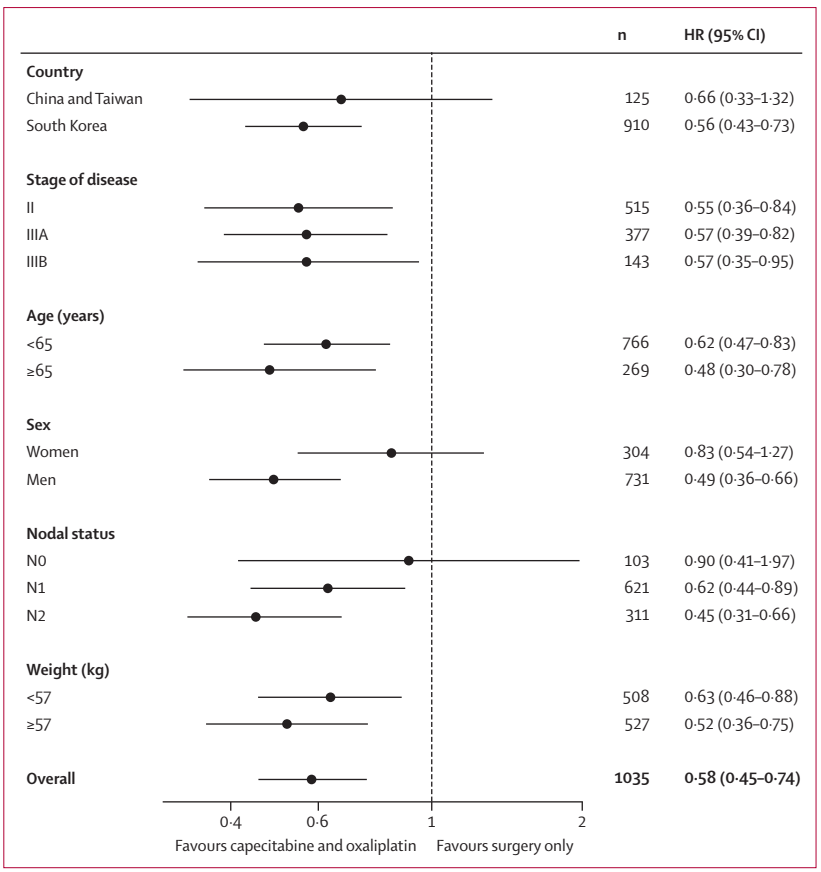


Figure 3: 3 year disease-free survival by stratification and prognostic factors in the intention-to-treat population

	Surgery alone (n=478)		Capecitabine and oxaliplatin (n=496)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Patients with ≥1 adverse event	253 (53%)	30 (6%)	490 (99%)	279 (56%)
Nausea	20 (4%)	0 (0%)	326 (66%)	39 (8%)
Neutropenia	4 (<1%)	1 (<1%)	300 (60%)	107 (22%)
Decreased appetite	18 (4%)	1 (<1%)	294 (59%)	23 (5%)
Peripheral neuropathy	0 (0%)	0 (0%)	277 (56%)	12 (2%)
Diarrhoea	52 (11%)	1 (<1%)	236 (48%)	9 (2%)
Vomiting	16 (3%)	0 (0%)	191 (39%)	37 (7%)
Fatigue	11 (2%)	0 (0%)	156 (31%)	23 (5%)
Thrombocytopenia	0 (0%)	0 (0%)	130 (26%)	40 (8%)
Hand–foot syndrome	0 (0%)	0 (0%)	93 (19%)	5 (1%)
Asthenia	5 (1%)	0 (0%)	87 (18%)	10 (2%)
Abdominal pain	42 (9%)	2 (<1%)	85 (17%)	8 (2%)
Constipation	17 (4%)	0 (0%)	63 (13%)	1 (<1%)
Dizziness	25 (5%)	0 (0%)	64 (13%)	3 (<1%)
Stomatitis, all	0 (0%)	0 (0%)	59 (12%)	3 (<1%)
Weight decreased	13 (3%)	2 (<1%)	59 (12%)	1 (<1%)
Peripheral sensory neuropathy	0 (0%)	0 (0%)	50 (10%)	3 (<1%)

Data are n (%). *Patients who received at least one dose of capecitabine or oxaliplatin.

Table 2: Adverse events reported by ≥10% of patients (safety population*)

Before CLASSIC, the Japanese ACTS-GC trial was the only large randomised trial of adjuvant chemotherapy (1 year of the oral fluoropyrimidine S-1) after curative resection with D2 gastrectomy.[13] Our findings accord with the ACTS-GC trial, and together these studies show that adjuvant chemotherapy after D2 gastrectomy improves outcomes in patients with resectable gastric cancer (panel).

We used surgery only as the reference treatment for our trial because it was the appropriate choice when the CLASSIC trial was designed. At that time, no large-scale randomised trials supporting the use of adjuvant therapy after D2 surgery had been done. The findings of the ACTS-GC trial,[13] which established fluoropyrimidine monotherapy as an effective adjuvant regimen after D2 surgery, were reported in 2007, after recruitment for the CLASSIC trial had begun. Both postoperative chemoradiotherapy and perioperative chemotherapy have been adopted as standard treatments in the USA and Europe, but their relevance after D2 surgery is unknown.

The frequency, severity, and type of adverse events documented with capecitabine and oxaliplatin in the CLASSIC study were consistent with the safety profile reported with adjuvant capecitabine and oxaliplatin in colon cancer.[28,29] In our study more than half of patients who received chemotherapy had peripheral neuropathy—a cumulative, dose-related toxic effect associated with oxaliplatin—although grade 3 or 4 events were infrequent. Most patients needed dose modifications because of adverse events, the most common being neutropenia, nausea, and vomiting. Capecitabine, should be started at the recommended dose with prompt dose modifications as needed for emergent adverse events.

A key question about our trial, as with any trial done in one geographical region, is how generalisable the findings are to other regions where disease management practices might differ. The CLASSIC trial had good patient outcomes; the 3 year overall survival rate in the surgery only group was substantially higher than that in the US Intergroup-0116 and UK MAGIC populations (78% in CLASSIC *vs* 30–40% in Intergroup-0116 and MAGIC).[14,15] Although our patient population had fewer T3 and T4 lesions than did US and European gastric cancer populations (44% in CLASSIC *vs* 68% in Intergroup-0116 *vs* 64% in MAGIC),[14,15] node-positive disease was more frequent (90% *vs* 85% *vs* 72%).[14,15] The difference in outcomes seems unlikely to be due to prognostic disparities, although the possibility of intrinsic biological differences in gastric cancer by region has been suggested.[30] Instead, we suggest that the favourable outcomes in our study are a result of the consistent use of D2 surgery and the high quality of that surgery (ensured by prospectively defined standard operating procedures and sampling of at least 15 lymph nodes). Now that D2 gastrectomy is standard of care in both Europe[10] and the USA,[11] our study findings could be highly relevant for, and might be generalisable to, other regions when D2 surgery is done by experienced surgeons.

On the basis of our findings, we suggest that a trial of capecitabine and oxaliplatin plus trastuzumab after D2 gastrectomy in patients with human epidermal growth factor receptor (HER)-2-positive operable disease is warranted. Such a study would build on the ToGA trial,[31] which showed improved overall survival with trastuzumab plus chemotherapy in patients with HER-2-positive advanced disease.

In conclusion, findings from the CLASSIC trial support the use of adjuvant capecitabine and oxaliplatin as a new treatment option for patients with resectable disease.

Panel: Research in context

Systematic review

A meta-analysis from the GASTRIC group based on individual patient data from 17 randomised clinical trials[12] showed that adjuvant chemotherapy with a fluorouracil-based regimen improves overall survival and disease-free survival compared with surgery only. However, the type of gastrectomy used in the studies was not standardised. D2 gastrectomy is now recommended in US[11] and European[10] treatment guidelines, and is widely used in east Asia as the preferred type of surgery for patients with operable gastric cancer. However, the benefits of adjuvant chemotherapy after this more extensive type of resection were uncertain. To address this question, two phase 3 trials were initiated (ACTS-GC and CLASSIC). The ACTS-GC trial showed a survival benefit with adjuvant fluoropyrimidine monotherapy after D2 gastrectomy compared with surgery only.[13]

Interpretation

The CLASSIC trial shows that adjuvant therapy with capecitabine and oxaliplatin improves 3 year disease-free survival after D2 gastrectomy compared with D2 gastrectomy only. Improved overall survival was also evident after only 3 years, although the data are immature and patient follow-up is ongoing. Together, the ACTS-GC and CLASSIC trials show that fluoropyrimidine-based adjuvant therapy improves outcomes after D2 gastrectomy in patients with operable gastric cancer.

Contributors

All authors had access to all the study data, analysed data, interpreted data, and reviewed, edited and approved the report for publication. Y-JB and SHN designed the study. Y-JB, Y-WK, H-KY, HCC, Y-KP, KHL, K-WL, YHK, S-IN, JYC, YJM, YHK, JFJ, T-SY, and SHN recruited patients and collected data. PB undertook the statistical analysis.

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Conflicts of interest

PB was employed by Roche Products Australia at the time of the study and is currently employed by Infopeople. FS is employed by F Hoffmann-La Roche and owns stock in the company. Y-JB has acted as a consultant for F Hoffmann-La Roche and Sanofi-Aventis, and has received honoraria from F Hoffman-La Roche. YHK has received honoraria and acted as a consultant for F Hoffman-La Roche and Sanofi-Aventis. The other investigators declare that they have no conflicts of interest.

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