Cohort Study

INTERNATIONAL JOURNAL OF SURGERY ONCOLOGY

OPEN

Trimodality therapy for resectable gastric cancer: analysis of the benefit in radiation

Balkarn S. Thind, MS, Thomas D. Mullen, MD, PhD, Erin Healy, MD, Nicholas Serrano, MS, Diana M. Christensen, MS, Trevor T. Miller, MS, Jing Zeng, MD, Brant K. Oelschlager, MD, Shilpen A. Patel, MD

Background: Gastric cancer is a common cause of cancer mortality worldwide, and due to its often advanced stage at the time of diagnosis, surgery alone is often inadequate treatment. Both chemotherapy (CH) and chemoradiation therapy (CHR) are used in the adjuvant setting and are both supported by randomized clinical trials. In this report, we compare the overall survival (OS), disease-free survival (DFS), and treatment toxicities of multimodal therapy with and without radiation.

Patients and methods: Data from 193 patients diagnosed with stage IB-III gastric cancer treated with surgery (S group), surgery plus chemotherapy (S + CH group), or surgery plus chemoradiation (S + CHR group) were retrospectively analyzed. OS, DFS, and toxicities were compared in the various treatment modalities.

Results: The S + CH (N = 69) and S + CHR group (N = 92) both had significant reduction in hazard ratio (HR) of death (HR, 0.24; $P < 0.001$; HR, 0.33; $P < 0.001$, respectively) when compared with the S group (N = 32). Although S + CHR showed no significant benefit in OS or DFS ($P = 0.73$, 0.16, respectively) when compared with S + CH, in a subgroup of patients with clinically lymph node–positive disease, S + CHR had significant improvement in DFS (HR, 1.83; $P = 0.047$). Significantly higher rates of esophagitis were observed in the S + CHR, but no significant difference in grade 3 to 4 hematologic toxicities. One treatment related death was recorded in S + CH from postsurgical grade 5 sepsis. The clinical nodal classification was borderline significantly different between the S + CH and S + CHR groups ($P = 0.05$) with a greater percentage of the S + CHR group being node positive.

Conclusions: Multimodal therapy was associated with improved OS in our report when compared with surgery alone. Although patients who received CHR along with surgery did not have a significant difference in OS or DFS when compared with those receiving only chemotherapy with surgery, there was a difference in DFS in those patients who were clinically lymph node positive.

Keywords: Gastric cancer, Therapy for gastric cancer, Radiation benefit, Gastric cancer undertreatment

Introduction

Gastric cancer is the fifth most common cancer worldwide and is the third leading cause of cancer-related death[1]. The National Cancer Institute estimates that in 2016, 26,370 Americans will be newly diagnosed with gastric cancer and that 10,730 will ultimately die from it[1,2]. Although mortality from gastric cancer is relatively low in the United States (14th most frequent cause of cancer mortality), it is far more common in other parts of the world, particularly in East Asia, Scandinavia, Central Europe, and Central and South America[1]. Although the overall incidence of gastric cancer is decreasing (by 1.5% each year for past 10 y)[1], the prognosis is often unfavorable[3].

Today, there is overwhelming consensus that surgical resection should be the backbone of curative therapy of gastric and gastroesophageal junction carcinoma[4–6]. However, risks of local recurrence and distant metastatic disease remain high after resection of most locally advanced tumors. Thus, there has been much interest in developing strategies to improve outcomes particularly with the introduction of chemotherapy and radiation therapy. An early study by Hazard and colleagues established a role for radiation therapy in improving locoregional control. The British Stomach Cancer Group randomly assigned 436 patients who had undergone gastric resection for stage II and III disease to no further therapy, adjuvant external-beam radiotherapy, or adjuvant chemotherapy. Five-year locoregional recurrence was significantly lower in the adjuvant external-beam radiotherapy arm when compared with surgery alone, 10% versus 27%, respectively[7].

Attention has also turned to adjuvant chemotherapy and multiple meta-analyses have demonstrated a modest benefit in overall survival (OS), if any, for adjuvant chemotherapy[8–12]. For example, Janunger and colleagues showed a significant OS benefit with adjuvant chemotherapy after surgery (odds ratio, 0.84; 95% CI, 0.74-0.96). More recently, however, the British MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) study by Cunningham and colleagues, demonstrated a significant OS benefit that favored a perioperative chemotherapy regimen including epirubicine, cisplatin, and continuous infusion 5-flurouracil (5-FU), also known as ECF, versus surgery alone[13].

As relapses after curative resection of gastric cancer can occur locally, regionally, and distally[14–16], combined chemotherapy and radiation therapy in the adjuvant setting could achieve better

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

University of Washington School of Medicine, Seattle, WA

Corresponding author. Address: 12611 25th Ave. SE, Everett, WA 98208. Tel: +206 9415013. E-mail address: thindb@uw.edu (B. S. Thind).

International Journal of Surgery Oncology (2017) 2:e06

Received 20 November 2016; Accepted 21 November 2016

Published online 4 January 2017

http://dx.doi.org/10.1097/IJ9.0000000000000006

control of microscopic disease both locally and distally. For example, the Intergroup 0116 study by MacDonald and colleagues showed a significant benefit in OS with adjuvant chemoradiotherapy (CHR) versus surgery alone (S)[17]. These investigators used a combination of adjuvant and concurrent 5-FU/leucovorin chemotherapy with conventionally fractionated radiation therapy to 45 Gy.

Although both the Cunningham and MacDonald studies described improved mortality rates for the use of multimodal therapy versus surgery alone, no phase III comparison of OS and disease-free survival (DFS) was made between patients receiving chemotherapy and surgery (S + CH) versus patients receiving chemoradiotherapy and surgery (S + CHR) until the ARTIST trial. They compared postoperative treatment with 6 cycles of capecitabine plus cisplatin (XP regimen) versus 2 cycles of XP followed by 45 Gy radiotherapy and 2 more cycles of XP. The trial concluded that S + CHR offered no significant reduction in recurrence when compared with S + CH; OS was not analyzed due to the small number of events[18]. The authors also called for further subgroup investigation to establish if radiation confers any benefit in OS and DFS.

The goals of this retrospective study are: (1) to compare OS between the S group and S + CH group, (2) to compare OS between the S group and S + CHR group, (3) to compare the OS and DFS between the S + CH group and S + CHR group, and (4) to compare toxicities of the different treatment modalities.

Methods

Eligibility

After obtaining approval from the Institutional Review Board, patient data were obtained from pathology databases, treatment and billing records, and tumor registries from the University of Washington Medical Center, Harborview Medical Center, and the Seattle Cancer Care Alliance, Seattle, WA. Patients who had been diagnosed and treated for resectable gastric or gastroesophageal junction adenocarcinoma stage IB-III (according to the AJCC Cancer Staging Manual 7th Edition)[19] between January 1999 through June 2016 were included in our analysis. Patients were excluded if they had in situ gastric adenocarcinoma, previous malignancies, or concurrent malignancies, and patients who had received treatment as a palliative rather than a curative measure.

Data collection

The patients were followed through June 2016 or most recent follow-up. The following information from patients' medical records was collected for our analyses: demographic data, date of diagnosis, cancer stage at diagnosis, tumor stage, nodal involvement, histology, treatment modality, treatment toxicities, and recurrence/mortality status. To determine the date of death for a deceased patient, we accessed their chart followed by the Social Security Death Index. Clinical Staging data were obtained from endoscopy, computed tomography, and positron emission tomography/computed tomography reports. Pathologic staging data were obtained from pathology reports.

Treatment modalities

Surgery only (S)

Details of the surgery were obtained from surgical operative reports. The procedures varied from subtotal to total gastrectomy with or without pancreatosplenectomy.

Surgery and chemotherapy (S + CH)

The majority of patients received either epirubicin, oxaliplatin, and capecitabine (EOX regimen) (52%), or ECF regimen (32%) with 3 cycles given before surgery and 3 cycles after surgery. Epirubicin and platinum-based chemotherapeutics were the most common agents administered.

Surgery and chemoradiation (S + CHR)

The majority of patients received leucovorin and continuous infusion 5-FU (MacDonald regimen) (46%). Other common regimens included carboplatin/paclitaxel (26%) and EOX (18%). The patients who received radiation therapy most commonly received radiation to 45 Gy.

Statistical analysis

The primary endpoints of this report were OS and DFS in the 2 multimodal groups. Key secondary endpoints included treatment toxicity and correlation of nodal status with treatment regimen. A subgroup analysis was conducted on clinically node-positive patients from both multimodal groups with the endpoints of OS and DFS. OS was defined as time from diagnosis to death, or last follow-up date, where patients were censored. DFS was defined as time from diagnosis to recurrence, second primary cancer, or death, whichever occurred first. For our analysis we calculated 2-, 3-, and 5-year survival rates, created Kaplan-Meier Survival curves to estimate median survival times, and hazard ratios (HRs) with confidence intervals of 95%. The log-rank test was used for univariate analysis, and a Cox regression was used for multivariate analysis, with sex, race, cancer stage at time of surgery, and age at diagnosis as covariates. Treatment toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.02. χ^2 test was used to compare the toxicities and the nodal status between S + CH and S + CHR. We used SPSS Version 21.0 (SPSS Inc., Chicago, IL) and considered $P < 0.05$ as significant for our results.

Results

Patient characteristics

Between January 1999 to June 2016, 193 patients met our inclusion criteria including 62 women (32%) and 131 men (68%). Ages ranged from 29 to 93 years, with a mean age of 60 years. Most patients were either white (N = 130, 67%) or Asian/Pacific Islander (N = 27, 14%). Sixty-three patients (33%) had node-negative disease and 130 patients (67%) had node-positive disease. Patient baseline characteristics for each treatment modality are summarized in **Table 1**.

Table 1

Patient demographics and characteristics.

Characteristics	N (%)		
	S (n = 32)	S + CH (n = 69)	S + CHR (n = 92)
Age (y)			
Median	70	58	60
Range	48-93	29-81	32-85
Sex			
Male	20 (63)	41 (60)	70 (76)
Female	12 (38)	28 (40)	22 (24)
Race			
White	18 (56)	43 (62)	69 (75)
African America	1 (3)	4 (6)	3 (3)
Asian	3 (9)	14 (20)	10 (11)
Hispanic/Latino	1 (3)	2 (3)	2 (2)
Other	9 (28)	6 (9)	8 (9)
Primary tumor site			
Gastric	17 (53)	25 (36)	42 (46)
GE junction	15 (47)	44 (64)	50 (54)
Stage grouping			
1B	9 (28)	11 (16)	12 (13)
II	9 (28)	28 (41)	63 (68)
III	14 (44)	30 (43)	17 (19)
T stage			
T1 or T2	17 (53)	24 (35)	34 (37)
T3	13 (41)	43 (62)	54 (59)
T4	2 (6)	2 (3)	4 (4)
Regional lymph nodes classification			
N0	10 (31)	30 (44)	23 (25)
N1	15 (47)	21 (30)	44 (48)
N2	6 (19)	15 (22)	18 (20)
N3	1 (3)	3 (4)	7 (8)
Chemotherapy regiment	NA		
Other*		4 (6)	6 (7)
5-FU/Leucovorin (MacDonald)		3 (4)	42 (46)
Leucovorin/5-FU/Oxaliplatin (FOLFOX)		4 (6)	3 (3)
Epirubicin/Oxaliplatin/Capecitabine (EOX)		36 (52)	17 (18)
Epirubicin/Cisplatin/5-FU (ECF)		22 (32)	0 (0)
Carboplatin/Paclitaxel		0 (0)	24 (26)

5-FU indicates 5-flurouracil; NA, not applicable; S, surgery group; S + CH, surgery plus chemotherapy group; S + CHR, surgery plus chemoradiation therapy.
*The principle regimen modified due to side effects.

S versus S + CH

These 2 groups were similar in terms of sex. The S group had generally older patients, more patients identifying their race as "other," and had earlier stages of cancer.

S versus S + CHR

These 2 groups were similar in terms of lymph node classification. The S group had generally older patients, more patients identifying their race as "other," greater percent of stage 1 and stage 3 cancer, and greater percentage of women when compared with the S + CHR group.

S + CH versus S + CHR

These were similar in age, race, tumor site, and T stage ($P = 0.84$) but different in sex and primary tumor classification. The lymph node classification (secondary endpoint) was borderline significant with 56.5% of the S + CH group having N1 to N3 positive disease and 75.0% of the S + CHR group having N1 to N3 positive disease ($P = 0.05$).

Toxicity

An important goal of this study was to compare the toxicity profiles between the S + CH and S + CHR groups. The most common adverse events for the S + CH group were grade 1 or 2 nausea (75.4%), fatigue (58.0%), vomiting (34.8%), and hand foot syndrome (26.1%); for the S + CHR group were nausea (67.4%), fatigue (58.7%), vomiting (29.3%), and esophagitis (28.3%). Hematological grade 3 to 4 adverse events included neutropenia, and thromboembolic events, each occurring at similar rates (χ^2 $P = 0.88$, 0.87, respectively in both treatment groups (**Table 2**). Nonhematologic grade 3 or 4 adverse events included nausea, vomiting, diarrhea, mucositis, esophagitis, and skin effects. Grade 3 or 4 esophagitis occurred in 17.4% of the patients in S + CHR and 1.4% of the patients in S + CH ($P = 0.001$). One treatment related death was recorded during the study in the S + CH group. The patient died from a postsurgical infection leading to grade 5 sepsis.

Efficacy

After a median follow-up time of 31.7 months, there were 79 deaths (15 in the S group, 24 in the S + CH group, and 40 in the S + CHR group) and 63 recurrence events (34 in the S + CH group and 29 in the S + CHR group).

Overall survival

The 2-year survival rates were 35.0% (95% CI, 13.6%-57.2%), 78.3% (95% CI, 64.7%-87.2%), and 67.5% (95% CI, 55.7%-76.8%) for the S, S + CH, and S + CHR groups, respectively. The 3-year survival rates were 28.0% (95% CI, 9.3%-50.6%), 61.7% (95% CI, 46.2%-74.0%), and 61.0% (95% CI, 48.7%-71.2%) for the S, S + CH, and S + CHR groups, respectively. The 5-year survival rates were 18.7% (95% CI, 3.7%-42.4%), 48.0% (95% CI, 31.2%-62.9%), and 49.2% (95% CI, 35.7%-61.4%) for the S, S + CH, and S + CHR groups, respectively. The median survival was 15.3, 53.5, and 50.2 months for the S, S + CH, and S + CHR groups, respectively (**Fig. 1**). The HR for death in the S group, as compared with the S + CH group, was 3.16 (95% CI, 1.65-6.05; $P < 0.001$), and the significance was retained in multivariate analysis with a HR of 4.12 (95% CI, 2.12-8.01; $P < 0.01$). The HR for death in the S group, as compared with the S + CHR group, was 2.87 (95% CI, 1.57-5.25; $P < 0.001$), and significance was again retained in multivariate analysis with a HR of 3.03 (95% CI, 0.67-1.75; $P < 0.001$). The third comparison was 1 of the 2 primary endpoints of this study; the HR for death in the S + CH group, as compared with S + CHR, was 0.91 (95% CI, 0.55-1.59; $P = 0.73$), the insignificance was retained in multivariate analysis ($P = 0.79$).

Disease-free survival

The second primary endpoint of this study was DFS in the 2 multimodal groups. The median duration of relapse-free survival was 25.3 months for the S + CH group and 75.0 months for the S + CHR group (**Fig. 2**). The HR of relapse in the S + CH group, as compared with the S + CHR group, was 1.79 (95% CI, 1.09-2.94;

Table 2

Toxicity profiles (all grades).

	N (%)	
Adverse Events	**S + CH**	**S + CHR**
Hematologic		
Neutropenia		
Grade 1 or 2	15 (21.1)	22 (23.9)
Grade 3 or 4	18 (26.1)	23 (25.0)
Thrombocytopenia		
Grade 1 or 2	1 (1.4)	4 (4.3)
Grade 3 or 4	0 (0.0)	1 (1.1)
Thromboembolic event		
Grade 1 or 2	0 (0.0)	0 (0.0)
Grade 3 or 4	2 (2.9)	0 (0.0)
Nonhematologic		
Nausea		
Grade 1 or 2	52 (75.4)	62 (67.4)
Grade 3 or 4	4 (5.8)	6 (6.5)
Vomiting		
Grade 1 or 2	24 (34.8)	27 (29.3)
Grade 3 or 4	1 (1.4)	4 (4.3)
Diarrhea		
Grade 1 or 2	14 (20.3)	16 (17.4)
Grade 3 or 4	1 (1.4)	0 (0.0)
Fatigue		
Grade 1 or 2	40 (58.0)	54 (58.7)
Grade 3 or 4	0 (0.0)	0 (0.0)
Mucositis		
Grade 1 or 2	5 (7.2)	9 (9.8)
Grade 3 or 4	1 (1.4)	1 (1.1)
Esophagitis		
Grade 1 or 2	1 (1.4)	26 (28.3)
Grade 3 or 4	1 (1.4)	16 (17.4)
Skin effects		
Grade 1 or 2	3 (4.3)	13 (14.1)
Grade 3 or 4	0 (0.0)	5 (5.4)
HFS		
Grade 1 or 2	18 (26.1)	17 (18.5)
Grade 3 or 4	0 (0.0)	1 (1.1)
Peripheral Neuropathy		
Grade 1 or 2	15 (21.7)	13 (14.1)
Grade 3 or 4	0 (0.0)	0 (0.0)

HFS indicates hand foot syndrome; S + CH, surgery plus chemotherapy group; S + CHR, surgery plus chemoradiation therapy.

$P = 0.02$). The significance, however, was not retained in multivariate analysis when age, stage, and race were used as covariates (HR, 1.47; 95% CI, 0.85-2.55; $P = 0.16$). Stage remained the only significant predictor of DFS on multivariate analysis; the HR of relapse in stage II disease, as compared with stage IB disease, was 4.382 (95% CI, 1.29-14.83; $P = 0.02$), in stage III disease, as compared with stage IB, was 6.58 (95% CI, 1.93-22.39; $P < 0.01$).

Subgroup analysis

Clinically node-positive patients from the S + CH and S + CHR groups were analyzed for OS and DFS. There was no significant difference in OS between the 2 multimodal groups ($P = 0.72$). The median DFS for clinically node-positive patients in the S + CH and S + CHR groups was 16.2 and 75.0 months, respectively. The HR of relapse in the clinically node-positive S + CH patients, as compared with clinically node-positive S + CHR patients was 2.58 (95% CI, 1.48-4.50; $P < 0.01$). The significance was retained in multivariate analysis with stage and treatment group as covariates (HR, 1.83; 95% CI, 1.01-3.33; $P = 0.047$).

Discussion

Overall, this study demonstrated that chemotherapy with or without concurrent radiation after surgery was well tolerated in the treatment of gastric cancer. A significant ($P = 0.001$) increase in grade 3 or 4 esophagitis was seen in the S + CHR group when compared with the S + CH group.

The addition of an adjuvant therapy, whether chemotherapy or CHR, for the treatment of gastric cancer, is associated with a near 76% reduction in mortality for the S + CH group and a 66% reduction in the S + CHR group, when compared with surgery only. Although no statistically significant mortality difference was observed between the S + CH and S + CHR groups, further analyses should be conducted before definitively determining that mortality rates are truly the same for both S + CH and S + CHR interventions. In the Cunningham and colleagues study, the S + CH patients' 5-year OS rate was 36% versus 23% for the surgery-only (S) patients, and the HR for death was 0.74[13]. The S + CH patients in the current study had a greater difference in 5-year OS rates compared with the S group patients (48.0% and 18.7%, respectively), and had a lower relative risk for death of 0.24 (95% CI, 0.12-0.47; $P < 0.001$). As this study is retrospective, there was likely patient selection bias, meaning patients who were healthier were more likely to receive adjuvant therapy, hence the larger difference between surgery and S + CH groups. In the Macdonald and colleagues study, the S + CHR patients' 3-year OS rate was 50% versus 41% for the S group patients, and the HR for death was 0.74[17]. The S + CHR group in this study had a greater difference in 3-year OS rates as compared with the S group patients (61.0% and 28.0%, respectively), and had a lower relative risk of death at 0.33 (95% CI, 0.18-0.62; $P < 0.001$). Again, the difference can likely be attributed to patient selection.

One concerning aspect among our population was that many of the patients had stage II-III disease and yet were not given preoperative or adjuvant therapy (S group), which should have been the standard after MacDonald and colleagues and Cunningham and colleagues. This may have been due to preexisting comorbidities precluding additional therapy. Recent studies have demonstrated the undertreatment of resected gastric cancer. Enestvedt et al[20] concluded that 63.2% of the potentially eligible patients did not receive CHR. Snyder et al[21] concluded that the rates of perioperative and postoperative CHR in patients with resected gastric cancer remains remarkably low. The surgery-only patients in our study were generally older and thus may have been less fit for preoperative or adjuvant therapy. Future efforts should focus on identifying and removing barriers to receive adjuvant therapy following resection.

The primary endpoints of this study were OS, addressed above, and DFS. A log-rank analysis of the recurrence rates showed a significant reduction in recurrence risk, HR 0.56 ($P = 0.02$), associated with the use of S + CHR compared with S + CH. Statistical significance was lost when a multivariate analysis was applied controlling for stage ($P = 0.16$). This suggests that an imbalance in stages between treatment groups accounts somewhat for the difference in DFS. For example, 43% versus 19% of

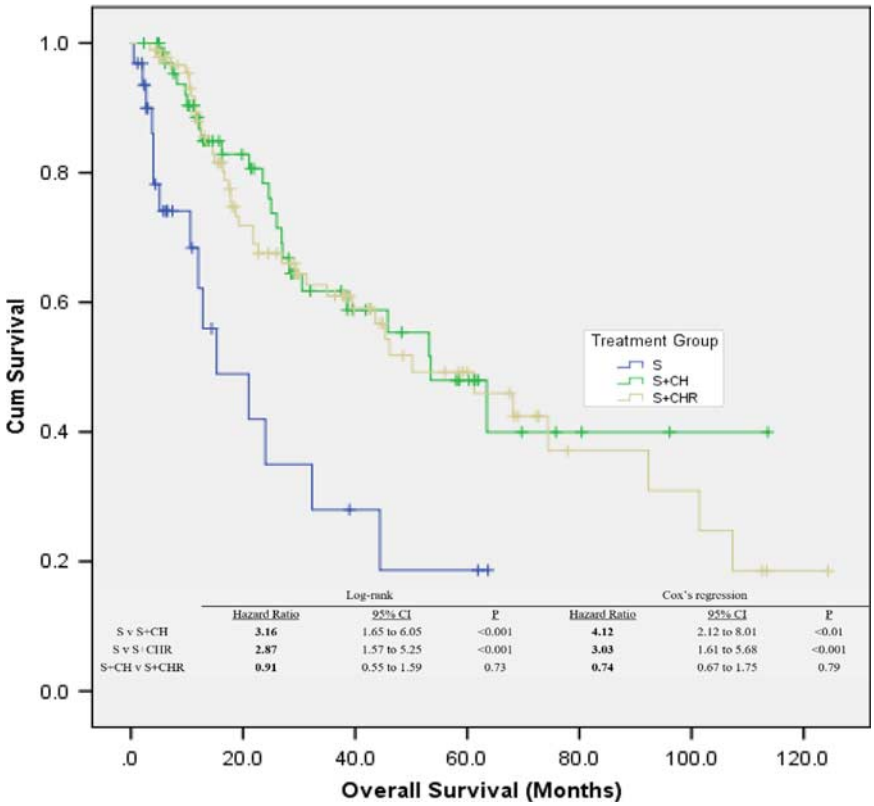


Figure 1. Overall survival of all patients, according to treatment. Hazard ratio analysis (bottom). CI indicates confidence interval; S, surgery only; S + CH, surgery plus chemotherapy; S + CHR, surgery plus chemoradiation.

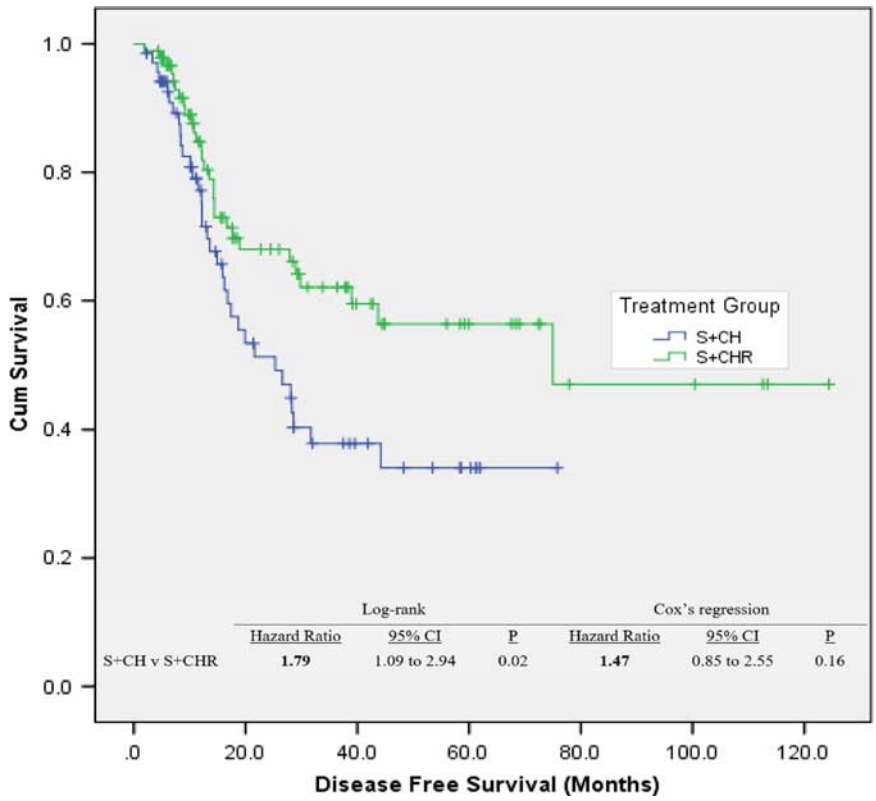
patients were stage III in the S + CH and S + CHR arms, respectively ($P < 0.01$). This lack of DFS benefit is not unexpected, as the ARTIST trial showed that the addition of radiation to chemotherapy did not significantly prolong DFS. Although a lack of efficacy could account for these results, Lee and colleagues postulate the limitation of their study due to low number of events. A recently accepted abstract from the CRITICS trial by Verheij et al, a phase III randomized study comparing preoperative chemotherapy with either postoperative chemotherapy or CHR, showed similar DFS rates between the 2 groups[22]. They reported 5-year survival rates of 40.8% for S + CH and 40.9% for S + CHR. They also noted that only 47% and 52% of the patients completed postoperative CH and CHR therapy, respectively, which could have affected the efficacy. Although these recent studies have shown insignificant benefit in the use of radiation in the adjuvant setting, both groups, ARTIST and CRITICS, call for further testing and suggest that preventing locoregional recurrence should be emphasized. In terms of OS and DFS, this study is in line with the most current randomized trials.

Although there was no significant improvement in OS or DFS in the S + CHR group when compared with the S + CH group, there was a statistically significant prolongation of DFS in the clinically node-positive subgroup analysis ($P = 0.047$). These results support the findings in the ARTIST trial, which also conducted a similar subgroup analysis that showed significant DFS improvement in the S + CHR group[18]. Because our subgroup was clinically node positive while the ARTIST trial subgroup was pathologically node positive, comparisons should be cautioned. The ARTIST II trial will explore this further by comparing CH versus CHR in patients with D2 lymph node dissection and pathologic lymph node–positive disease[23].

A key secondary endpoint looked for a correlation between initial clinical tumor staging and the treatment regimen (S + CH vs. S + CHR). T stage was similar between the S + CH and S + CHR groups ($P = 0.84$). The nodal classification was borderline significantly different between the S + CH and S + CHR groups ($P = 0.05$), which had 56.5% and 75.0% N1 to N3 disease, respectively. These data could reflect clinical judgment or the ARTIST trial results showing increased DFS with S + CHR in positive pathologic lymph node gastric cancer. Further studies could be performed with specific recruitment criteria to limit the confounding variables and investigate this borderline significance.

This study has several limitations. Gastric cancer is not prevalent in the United States and this fact was reflected in the number of patients in our study population. Our study is also retrospective in nature and selection bias confounds our analysis.

Apart from the controversy regarding the addition of adjuvant radiation in gastric cancer, trials are being conducted to address the optimal sequence of therapy. CRITICS II trial, phase II, will evaluate preoperative CH and CHR. ARTIST II trial will evaluate adjuvant CH and CHR in node-positive patients[23]. These and



	Log-rank			Cox's regression		
	Hazard Ratio	95% CI	P	Hazard Ratio	95% CI	P
S+CH v S+CHR	**1.79**	1.09 to 2.94	0.02	**1.47**	0.85 to 2.55	0.16

Figure 2. Disease-free survival of all patients, according to treatment. Hazard ratio analysis (bottom). CI indicates confidence interval; S + CH, surgery plus chemotherapy; S + CHR, surgery plus chemoradiation.

other ongoing prospective randomized trials could help refine clinical factors to determine the treatment modality and timing.

Our results show that multimodal therapy including chemotherapy or CHR for the treatment of resectable gastric cancer is associated with decreased mortality when compared with surgery alone, these results are consistent with findings from previous studies[13,17]. Multivariate analysis showed no significant difference in OS and DFS between the 2 multimodal groups, again, consistent with other studies[18,22]. Both modalities were well tolerated in our patient population.

References

[1] Ferlay J, Soerjomataram I, Dikshit R, *et al*. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.

[2] Howlader N, Noone AM, Krapcho M, *et al*. SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, Accessed April 2016.

[3] Hartgrink HH, Jansen EPM, van Grieken NCT, *et al*. Gastric cancer. Lancet Lond Engl 2009;374:477–90.

[4] Songun I, Putter H, Kranenbarg EM-K, *et al*. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010;11:439–9.

[5] Stein HJ, Feith M, Siewert JR. Cancer of the esophagogastric junction. Surg Oncol 2000;9:35–41.

[6] Van Cutsem E, Van de Velde C, Roth A, *et al*. Expert opinion on management of gastric and gastro-oesophageal junction adenocarcinoma on behalf of the European Organisation for Research and Treatment of Cancer (EORTC)-gastrointestinal cancer group. Eur J Cancer Oxf Engl 1990 2008;44:182–94.

[7] Hazard L, O'Connor J, Scaife C. Role of radiation therapy in gastric adenocarcinoma. World J Gastroenterol 2006;12:1511–20.

[8] Earle CC, Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. Eur J Cancer Oxf Engl 1990 1999;35:1059–64.

[9] Hermans J, Bonenkamp JJ, Boon MC, *et al*. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. J Clin Oncol 1993;11:1441–7.

[10] Janunger K-G, Hafström L, Glimelius B. Chemotherapy in gastric cancer: a review and updated meta-analysis. Eur J Surg Acta Chir 2002;168:597–608.

[11] Mari E, Floriani I, Tinazzi A, *et al*. Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomised trials. A study of the GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente). Ann Oncol 2000;11:837–43.

[12] Panzini I, Gianni L, Fattori PP, *et al*. Adjuvant chemotherapy in gastric cancer: a meta-analysis of randomized trials and a comparison with previous meta-analyses. Tumori 2002;88:21–7.

[13] Cunningham D, Allum WH, Stenning SP, *et al*. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11–20.

[14] Gunderson LL. Gastric cancer—patterns of relapse after surgical resection. Semin Radiat Oncol 2002;12:150–61.

[15] Marrelli D, Roviello F, de Manzoni G, *et al*. Different patterns of recurrence in gastric cancer depending on Lauren's histological type: longitudinal study. World J Surg 2002;26:1160–5.

[16] Schwarz RE, Zagala-Nevarez K. Recurrence patterns after radical gastrectomy for gastric cancer: prognostic factors and implications for postoperative adjuvant therapy. Ann Surg Oncol 2002;9:394–400.

[17] Macdonald JS, Smalley SR, Benedetti J, *et al*. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725–30.

[18] Lee J, Lim DH, Kim S, *et al*. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol 2012;30: 268–73.
[19] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th Edition of the AJCC Cancer Staging Manual and the Future of TNM. Ann Surg Oncol 2010;17:1471–4.
[20] Enestvedt CK, Diggs BS, Shipley DK, *et al*. A population-based analysis of surgical and adjuvant therapy for resected gastric cancer: are patients receiving appropriate treatment following publication of the intergroup 0116 results? Gastrointest Cancer Res 2009;3:233–8.
[21] Snyder RA, Penson DF, Ni S, *et al*. Trends in the use of evidence-based therapy for resectable gastric cancer. J Surg Oncol 2014;110: 285–90.
[22] Verheij M, Jansen EPM, Cats A. A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer: first results from the CRITICS study. J Clin Oncol 2016;34:(suppl; abstr 4000). http://meetinglibrary.asco.org/content/165706-176. Accessed August 15, 2016.
[23] Choi AH, Kim J, Chao J. Perioperative chemotherapy for resectable gastric cancer: MAGIC and beyond. World J Gastroenterol WJG 2015;21:7343–8.