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ABSTRACT

Purpose

After curative resection of gastric or gastroesophageal junction adenocarcinoma, Intergroup Trial 0116 (Phase III trial of postoperative adjuvant radiochemotherapy for high risk gastric and gastroesophageal junction adenocarcinoma: Demonstrated superior survival for patients who received postoperative chemoradiotherapy with bolus fluorouracil (FU) and leucovorin (LV) compared with surgery alone. CALGB 80101 (Alliance; Phase III Intergroup Trial of Adjuvant Chemoradiation After Resection of Gastric or Gastroesophageal Adenocarcinoma) assessed whether a postoperative chemoradiotherapy regimen that replaced FU plus LV with a potentially more active systemic therapy could further improve overall survival.

Patients and Methods

Between April 2002 and May 2009, 546 patients who had undergone a curative resection of stage IB through IV (M0) gastric or gastroesophageal junction adenocarcinoma were randomly assigned to receive either postoperative FU plus LV before and after combined FU and radiotherapy (FU plus LV arm) or postoperative epirubicin, cisplatin, and infusional FU (ECF) before and after combined FU and radiotherapy (ECF arm).

Results

With a median follow-up duration of 6.5 years, 5-year overall survival rates were 44% in the FU plus LV arm and 44% in the ECF arm ($P_{logrank}$ = .69; multivariable hazard ratio, 0.98; 95% CI, 0.78 to 1.24 comparing ECF with FU plus LV). Five-year disease-free survival rates were 39% in the FU plus LV arm and 37% in the ECF arm ($P_{logrank}$ = .94; multivariable hazard ratio, 0.96; 95% CI, 0.77 to 1.20). In post hoc analyses, the effect of treatment seemed to be similar across all examined patient subgroups.

Conclusion

After a curative resection of gastric or gastroesophageal junction adenocarcinoma, postoperative chemoradiotherapy using a multiagent regimen of ECF before and after radiotherapy does not improve survival compared with standard FU and LV before and after radiotherapy.

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INTRODUCTION

Surgical resection is the primary treatment of nonmetastatic gastric cancer, and the 5-year survival rate diminishes rapidly with increasing stage of disease. Among Western patients with localized lesions, the 5-year survival rate is 65%; however, for those with regional spread, estimated 5-year survival drops to 30%.[1-3] This poor prognosis among resected patients necessitates the evaluation of potentially promising adjuvant strategies.

In a US National Cancer Institute–sponsored randomized clinical trial of 556 patients who had undergone a curative resection of gastric or gastroesophageal junction adenocarcinoma—Intergroup Trial 0116 (Phase III trial of postoperative adjuvant radiochemotherapy for high risk gastric and gastroesophageal junction adenocarcinoma)—demonstrated a significant survival benefit with the use of adjuvant fluorouracil

(FU)-based chemoradiotherapy compared with surgery alone.[3,4] Of note, the benefit associated with the regimen seemed to be principally in the reduction of locoregional failure; differences in the rate of distant failure were less pronounced. As a consequence, subsequent trials have examined whether the use of multiagent chemotherapy regimens, potentially more systemically active than FU and leucovorin (LV), might further enhance the survival benefit associated with postoperative chemoradiotherapy.

In the absence of radiotherapy, the British MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) trial demonstrated the superiority of a combination of epirubicin, cisplatin, and FU (ECF) administered before and after surgical resection of gastric cancer compared with surgery alone.[5] Despite the omission of radiotherapy, perioperative ECF conferred a statistically significant reduction in death and cancer recurrence, establishing perioperative chemotherapy, without radiation therapy, as an alternative, reasonable standard in the treatment of resectable gastric cancer.

On the basis of these aforementioned trials, we hypothesized that the survival benefit offered by postoperative FU-based chemoradiation may be enhanced by replacing bolus FU plus LV with a potentially more active multi-agent chemotherapy regimen (ECF). Cancer and Leukemia Group B (CALGB 80101, now Alliance; Phase III Intergroup Trial of Adjuvant Chemoradiation After Resection of Gastric or Gastroesophageal Adenocarcinoma) was designed to compare a postoperative regimen of FU plus LV before and after radiotherapy, as developed in Intergroup Trial 0116, with a regimen of ECF before and after radiotherapy in patients who had undergone a curative resection of stage IB through IV (M0) gastric or gastroesophageal junction adenocarcinoma. Here we report an analysis of overall survival (OS) and disease-free survival (DFS) from CALGB 80101 completed after a median follow-up of 6.5 years.

PATIENTS AND METHODS

Eligibility Criteria

Patients were recruited on the basis of the following eligibility criteria: histologically confirmed stage IB through IV (M0) adenocarcinoma of the stomach or gastroesophageal junction, according to the 2002 (6th edition) staging criteria of the American Joint Commission on Cancer[6]; en bloc surgical resection of tumor without residual disease; an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2; adequate function of major organs (serum creatinine ≤ 1.5 mg/dL and bilateral renal function; serum bilirubin ≤ 2.0 mg/dL; serum AST ≤ 3 times the upper limit of normal; absolute neutrophil count $\geq 1,500/\mu$L; and platelet count $\geq 100,000/\mu$L); a caloric intake sufficient to ensure a stable weight (< 2 pounds weight loss) for at least 1 week before registration; and random assignment and treatment initiation no earlier than 21 days and no later than 84 days after surgical resection. All patients provided written institutional review board–approved, protocol-specific informed consent according to institutional and federal guidelines. An evaluation by a radiation oncologist was required before enrollment to ensure appropriateness for radiation therapy.

Study Design and Treatment

Eligible patients were randomly assigned 1:1 to receive a postoperative adjuvant regimen of FU plus LV before and after combined FU and radiotherapy, or ECF before and after radiotherapy. Stratification factors were depth of tumor penetration (T1/T2; T3; T4), nodal status (no positive nodes; one to three positive nodes; four or more positive nodes), and total number of lymph nodes examined in the surgical resection specimen (< 7; seven to 14; or ≥ 15).

Patients assigned to FU plus LV received bolus FU (425 mg/m^2 per day) and LV (20 mg/m^2 per day) for 5 days starting on day 1, followed by chemoradiotherapy, which began 28 days after the start of the initial cycle of chemotherapy. Four weeks after the completion of radiotherapy, two additional 5-day cycles of bolus FU (425 mg/m^2 per day) plus LV (20 mg/m^2 per day) were given 1 month apart.

Patients assigned to ECF received epirubicin (50 mg/m^2 on day 1), cisplatin (60 mg/m^2 on day 1), and FU (200 mg/m^2 per day continuous infusion for 21 days starting on day 1), followed by chemoradiotherapy beginning 28 days after the start of the initial cycle of chemotherapy. Four weeks after the completion of radiotherapy, two additional cycles of epirubicin (40 mg/m^2 on day 1), cisplatin (50 mg/m^2 on day 1), and FU 200 mg/m^2 per day continuous infusion for 21 days were given starting on day 1; each cycle was given 21 days apart.

In both arms, radiotherapy consisted of 45 Gy of radiation at 1.8 Gy per day, 5 days per week, for 5 weeks with continuous infusion FU (200 mg/m^2 per day, 7 days per week throughout radiation). Target radiotherapy volume was based on preoperative imaging, surgical findings, including the size and location of the primary lesion and pathologically involved lymph nodes, and location of surgical margins. Doses were limited to ensure that $< 30\%$ of the liver was exposed to > 30 Gy, two thirds or more of one functioning kidney was not irradiated, $< 50\%$ of the combined volume of the right and left ventricles of the heart received > 25 Gy, and the spinal cord received < 45 Gy. In general, for patients with node-positive gastric tumors, radiation covered the tumor bed, residual stomach, resection margins, and nodal drainage regions. For node-negative gastric tumors with pathology evaluation of ≥ 10 nodes and surgical margins ≥ 5 cm, treatment of the nodal beds was not required. For tumors of the gastroesophageal junction, radiation fields extended into the chest approximately 5 cm proximal to the area of known esophageal involvement with an intent to fully treat periesophageal tissues at the level of the tumor.

Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 2.0), and doses of chemotherapy were reduced according to toxicity assessments as prescribed in the study protocol (Data Supplement).

Radiotherapy Quality Assurance

Prior approval of the radiotherapy treatment plan was required before treatment initiation by the Quality Assurance Review Center (now the Imaging and Radiation Oncology Core Rhode Island), and the radiation oncology study co-chairs (J.E.T. and H.J.M.). Treatment fields, dosimetry, surgery and pathology reports, and preoperative tumor imaging were submitted for review. Plans that were not approved were principally based on toxicity risks to critical organs or the failure to treat appropriate target volumes. At pretreatment review, 15% of treatment plans were found to contain a potential major protocol deviation, most of which were corrected before radiotherapy initiation. A final quality assurance review of radiotherapy (conducted after the delivery of radiation) revealed major deviations in 4% of the treatment plans.

Statistical Considerations

The primary end point of CALGB 80101 was OS, with DFS and adverse events as key secondary end points. Patients were only followed for first disease recurrence. Time to first disease recurrence was measured from study entry until documented recurrence of disease or last known follow-up. Assessment of treatment efficacy was performed on an intent-to-treat basis. Safety analyses included all patients who received at least one dose of study therapy.

The trial was originally designed for a planned enrollment of 824 patients with 80% power to detect a 25% improvement in OS among patients treated with ECF compared with those treated with FU plus LV, with a one-sided alpha at a significance level of .05. In August 2005, with all

data still masked to the investigators and with 171 patients randomly assigned, the protocol was amended to address slower than expected enrollment; total enrollment was changed to 540 patients, which provided 80% power to detect a 30% improvement in OS among patients treated with ECF compared with those treated with FU plus LV (an improvement in median survival from 3.0 to 3.9 years), on the basis of a one-sided, stratified (by the stratification factors used at random assignment) log-rank test at a significance level of .05. Formal interim analyses for superiority and futility were conducted after 20% of the expected deaths were observed and submitted for review by the CALGB Data and Safety Monitoring Board. Interim analyses were repeated approximately every 6 months thereafter. An adjusted test of significance for OS on the basis of the stratified log-rank test was used to test superiority of ECF versus FU; an adjusted, CI approach was used to exclude a log hazard ratio (HR) of 0.2624, corresponding to an HR of 1.3. The one-sided Lan-DeMets analog of the O'Brien-Fleming boundaries was used to adjust for multiplicity in both cases.[7]

Comparisons of OS and DFS between arms were performed using a one-sided, stratified log-rank test. OS was measured from study enrollment until death from any cause. DFS was measured from the date of study enrollment until death or documented second primary tumor, or cancer recurrence. HRs with 95% CIs were calculated using the Cox proportional hazards model. Multivariable analyses adjusted by patient and disease characteristics were also performed post hoc using the Cox regression model. Models were adjusted for age (years as a continuous variable); sex; race (white v black v other); ECOG performance status (0 v 1or 2); depth of tumor penetration (T1 or T2 v T3 or T4); histologic grade (well v moderately v poorly differentiated v undifferentiated); number of positive lymph nodes (0 v 1 to 3 $v \geq$ 4); number of nodes examined (< 7 v 7 to 14 $v \geq$ 15); site of tumor location (gastroesophageal junction v proximal stomach v distal stomach v multicentric v stomach not otherwise specified). Fifty patients with missing data on at least one of these variables were excluded from the analysis. Survival curves were estimated using the Kaplan-Meier method. In addition, analyses within patient subgroups were conducted post hoc using Cox regression models. Statistical interactions were represented by the cross-products of the corresponding variables. The statistical methods proposed by Gray[8] for the analysis of the cumulative incidence of competing risks were used to estimate the rates of locoregional versus distal first recurrence and

investigate the effect of treatment regimen on locoregional first recurrence versus distant metastases.[9]

Patient registration and data collection were managed by the Alliance (formerly CALGB) Statistics and Data Center. Data quality was ensured by careful review of data by Alliance Statistics and Data Center staff and by the study chairperson. All analyses were based on the study database frozen on February 19, 2016, and were performed by Alliance statisticians using SAS 9.2 (SAS Institute, Cary, NC) or R.

RESULTS

Baseline Characteristics

Between April 30, 2002, and May 29, 2009, 546 patients were randomly assigned to receive either FU plus LV before and after combined FU and radiotherapy (n = 280) or ECF before and after combined FU and radiotherapy (n = 266). Enrollment, treatment allocation, eligibility, follow-up, and the number of patients included in the final data analysis are shown in Figure 1. The Alliance Data and Safety Monitoring Board released the trial data after the eighth interim analysis, in which the futility boundary was nearly crossed and the conditional probability of observing a significant difference between treatment regimens was low. Baseline patient, disease, and prior treatment characteristics were largely similar between treatment arms (Table 1). A slightly higher proportion of patients in the ECF arm (62%) had $\geq$ 15 lymph nodes examined in the surgical resection specimen compared with the FU plus LV arm (50%).

Treatment Delivery

The median time to treatment initiation after surgical resection was 54 days for FU plus LV and 53 days for ECF. All planned postoperative adjuvant therapy was completed by 68% of patients
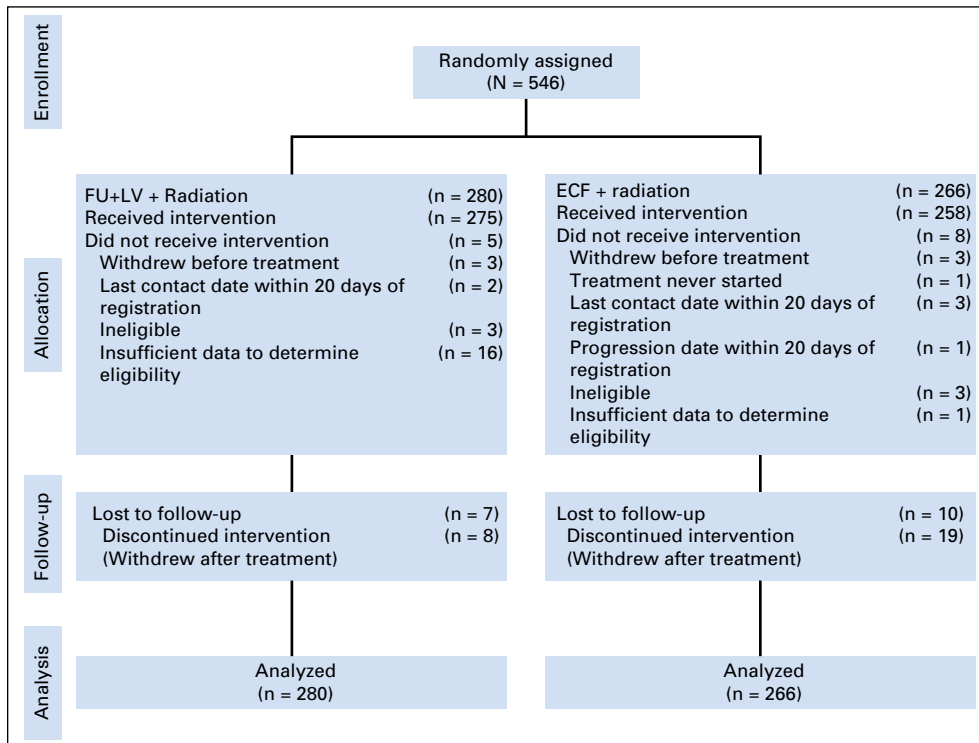

Fig 1. Flow diagram of all registered patients. ECF, epirubicin, cisplatin, and fluorouracil; FU, fluorouracil; LV, leucovorin.

Table 1. Baseline Patient Characteristics			
Characteristic	FU+LV (n = 280) No. (%)	ECF (n = 266) No. (%)	Overall (n = 546) No. (%)
Median age, years (range)	59 (23-81)	58 (29-83)	59 (23-83)
Sex			
Male	193 (69)	178 (67)	371 (68)
Female	87 (31)	88 (33)	175 (32)
Race			
White	214 (77)	189 (71)	403 (74)
Black	29 (10)	41 (15)	70 (13)
Asian	22 (8)	23 (9)	45 (8)
Other	15 (5)	13 (5)	28 (5)
ECOG performance status*			
0	132 (47)	144 (54)	276 (50)
1	139 (50)	118 (44)	257 (47)
2	9 (3)	4 (2)	13 (3)
Primary tumor location			
Gastroesophageal junction	65 (24)	55 (21)	120 (22)
Proximal gastric	16 (6)	7 (3)	23 (4)
Distal gastric	102 (37)	120 (45)	222 (41)
Stomach NOS	46 (17)	34 (13)	80 (15)
Multicentric	44 (16)	48 (18)	92 (17)
Unknown	7	2	9
Depth of tumor			
T1 or T2	124 (46)	128 (49)	252 (47)
T3	137 (50)	122 (46)	259 (48)
T4	12 (4)	11 (4)	23 (5)
Unknown	7	5	12
Number of involved lymph nodes			
0	42 (15)	35 (13)	77 (15)
1-3	91 (34)	93 (36)	184 (35)
≥ 4	137 (51)	133 (51)	270 (50)
Unknown	10	5	15
Number of lymph nodes examined			
< 7	35 (13)	26 (10)	61 (11)
7-14	100 (37)	75 (28)	175 (33)
≥ 15	137 (50)	162 (62)	299 (56)
Unknown	8	3	11
Histologic grade			
Well differentiated	7 (3)	8 (3)	15 (3)
Moderately differentiated	70 (26)	69 (26)	139 (26)
Poorly differentiated	188 (69)	172 (65)	360 (68)
Undifferentiated	6 (2)	11 (4)	17 (3)
Unknown	9	6	15

NOTE. Except for median age, all values are No. (%).
Abbreviations: ECF, epirubicin, cisplatin, and fluorouracil; ECOG, Eastern Cooperative Oncology Group; FU, fluorouracil; LV, leucovorin; NOS, not otherwise specified.
*Performance status evaluated according to guidelines of the ECOG, with a performance status of 0 indicating asymptomatic; 1, restricted in strenuous activity but ambulatory and able to do light work; or 2, ambulatory and capable of all self-care, but unable to work.

Table 2. Reasons for Treatment Cessation			
Reason	FU+LV (n = 280) No. (%)	ECF (n = 266) No. (%)	Overall (n = 546) No. (%)
Completed treatment	191 (68)	168 (63)	359 (66)
Progressive disease	14 (5)	7 (3)	21 (4)
Adverse event	24 (9)	40 (15)	64 (12)
Death	9 (3)	3 (1)	12 (2)
Withdrew after beginning treatment	8 (3)	19 (7)	27 (5)
Withdrew before beginning treatment	5 (1)	8 (2)	13 (2)
Alternative therapy	1 (0.4)	0 (0)	1 (0.2)
Other disease	2 (0.7)	3 (1)	5 (1)
Other	1 (0.4)	3 (1)	4 (1)

Abbreviations: ECF, epirubicin, cisplatin, and fluorouracil; FU, fluorouracil; LV, leucovorin.

arms, although rates of grade 4 or higher neutropenia was higher in the FU plus LV arm (34% v 19%, respectively). Adverse events that led to treatment modifications (delays or dose reductions) occurred in 57% of patients in the FU plus LV arm and 54% in the ECF arm.

Seven deaths (3%) were considered related to treatment in the FU plus LV group. The reported causes of death included colitis (n = 1), infection associated with neutropenia (n = 1), infection without neutropenia (n = 1), pneumonitis (n = 2), acute respiratory distress syndrome (n = 1), and cause unknown (n = 1). One death (< 1%) was considered related to treatment in the ECF group (gastrointestinal obstruction).

Efficacy

After a median follow-up duration of 6.5 years, 322 deaths were documented (170 in the FU plus LV arm and 152 in the ECF arm). The estimated 5-year OS rates were 44% in the FU plus LV arm and 44% in the ECF arm (stratified $P_{logrank}$ = .69; Fig 2A). With 358 DFS events observed (186 in the FU plus LV arm and 172 in the ECF arm), the estimated 5-year DFS rates were 39% in the FU plus LV arm and 37% in the ECF arm (stratified $P_{logrank}$ = .94; Fig 2B). Adjusting for other known or suspected predictors of patient outcome, the multivariable HR for mortality of 0.98 (95% CI, 0.78 to 1.24) for patients in the ECF arm, compared with those treated in the FU plus LV arm. The multivariable HR for cancer recurrence or mortality (DFS) was 0.96 (95% CI, 0.77 to 1.20) comparing treatment arms.

Subgroup Analyses

We further examined post hoc the effect of treatment according to strata of known or suspected predictors of cancer recurrence (Fig 3). Across each of these strata, there continued to be no significant survival benefit for patients treated in the ECF arm compared with those in the FU plus LV arm ($P_{interaction}$ > .005 on the basis of a Bonferroni-adjusted P value for 10 tests of interaction).

Pattern of Recurrence

Locoregional recurrence was defined as recurrence at the anastomotic site, duodenal stump, tumor bed, or remnant stomach

(191 of 280) in the FU plus LV arm and 63% (168 of 266) in the ECF arm (Table 2). A lower proportion of patients in the FU plus LV arm discontinued treatment because of an adverse event or treatment withdrawal than in the ECF arm (13% v 24%, respectively; P = .001).

Safety

The overall incidence of adverse events (any grade) was 98% in the FU plus LV arm and 94% in the ECF arm. Grade 3 or higher diarrhea, mucositis, and dehydration were each more common in the FU plus LV arm compared with the ECF arm (Table 3). Grade 3 or higher neutropenia rates were comparable between treatment

Table 3. Adverse Events at Least Possibly Related to Treatment, According to Grade

Event	FU+LV (n = 272), No. (%)		ECF (n = 251), No. (%)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Nausea	199 (73)	45 (17)	183 (73)	40 (16)
Diarrhea	171 (63)	39 (14)	125 (50)	17 (7)
Mucositis	170 (63)	41 (15)	109 (43)	20 (8)
Dehydration	40 (15)	27 (10)	33 (13)	13 (5)
Anorexia	154 (57)	42 (15)	141 (56)	34 (13)
Fatigue	207 (76)	29 (11)	194 (77)	33 (13)
Vomiting	126 (46)	25 (9)	121 (48)	27 (11)
Neutropenia	188 (69)	145 (53)	174 (69)	121 (48)
Grade ≥ 4 neutropenia	NA	92 (34)	NA	48 (19)
Febrile neutropenia	13 (5)	12 (4)	6 (2)	5 (2)

Abbreviations: ECF, epirubicin, cisplatin, and fluorouracil; FU, fluorouracil; LV, leucovorin; NA, not available.

or at the regional lymph nodes within the radiation field. Distant metastasis was defined as lymph node recurrence outside the radiation field, peritoneal seeding, liver metastasis, or metastasis to other extra-abdominal sites. To date, 257 patients experienced cancer recurrence (129 who received FU plus LV and 128 who received ECF). Data on location of cancer recurrence were available for 112 patients (61 who received FU plus LV, with 32 locoregional and 29 distal; 51 who received ECF, with 26 locoregional and 25 distal). No differences in the cumulative incidence of locoregional recurrences versus distant metastases were apparent overall (Appendix Fig A1A, online only). No significant differences were observed for either locoregional recurrences (P = .56) or distant metastases (P = .88) between treatment arms (Appendix Fig A1B). Two patients who died without evidence of recurrence were omitted from this analysis.
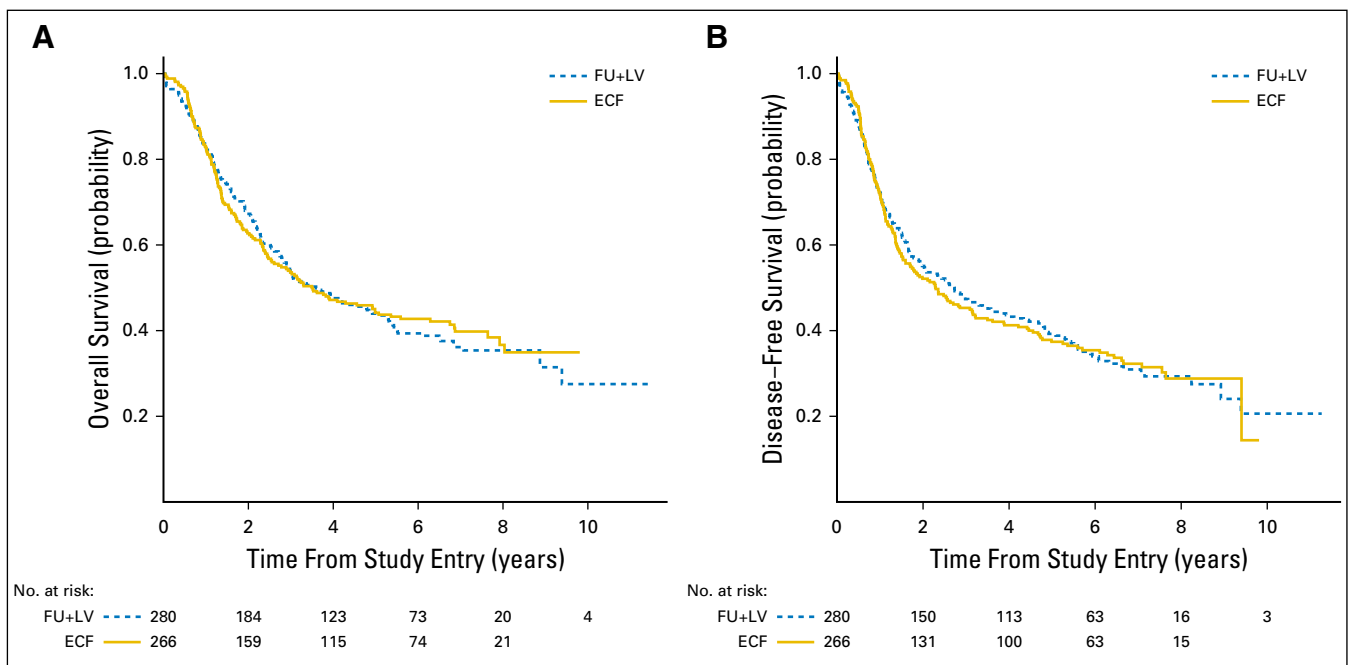
DISCUSSION

In this randomized clinical trial of patients who had undergone a curative resection of gastric or gastroesophageal junction adenocarcinoma, we sought to build on the survival benefit associated with adjuvant chemoradiotherapy in Intergroup Trial 0116[3,4] by replacing standard FU plus LV with the multiagent regimen of ECF, delivered before and after concomitant FU and radiotherapy. However, postoperative chemoradiotherapy with ECF before and after radiotherapy did not improve OS or DFS compared with a regimen of bolus FU plus LV before and after radiotherapy. We failed to observe any significant benefit associated with the ECF regimen within any specific patient subgroup, although the power to examine such interactions was limited.

Intergroup Trial 0116 was widely criticized for the limited lymph node dissections performed on patients enrolled in the study. Although several large randomized trials comparing D1 and D2 lymph node dissections in gastric cancer failed to demonstrate a significant OS benefit associated with the D2 dissection,[10-13] D2 lymphadenectomy has become a standard surgical approach in many centers.[14] In the current trial, only 55% of patients had ≥ 15 lymph nodes examined in the surgical resection specimen, and 11% of patients had fewer than seven lymph nodes examined. Nonetheless, there is no evidence that the extent of lymph node dissection influenced the relative benefit of ECF compared with FU plus LV. Our findings did not change when we examined relative treatment effects across different strata of number of lymph nodes examined.

Treatment-related toxicity could influence the efficacy of the individual adjuvant chemoradiotherapy regimens. However, treatment completions rates and rates of grade 3 or higher adverse events were comparable between the arms. Rates of grade 3 or higher gastrointestinal toxicities and grade 4 or higher neutropenia

Fig 2. (A) Overall survival by treatment arm. (B) Disease-free survival by treatment arm. ECF, epirubicin, cisplatin, and fluorouracil; FU, fluorouracil; LV, leucovorin.
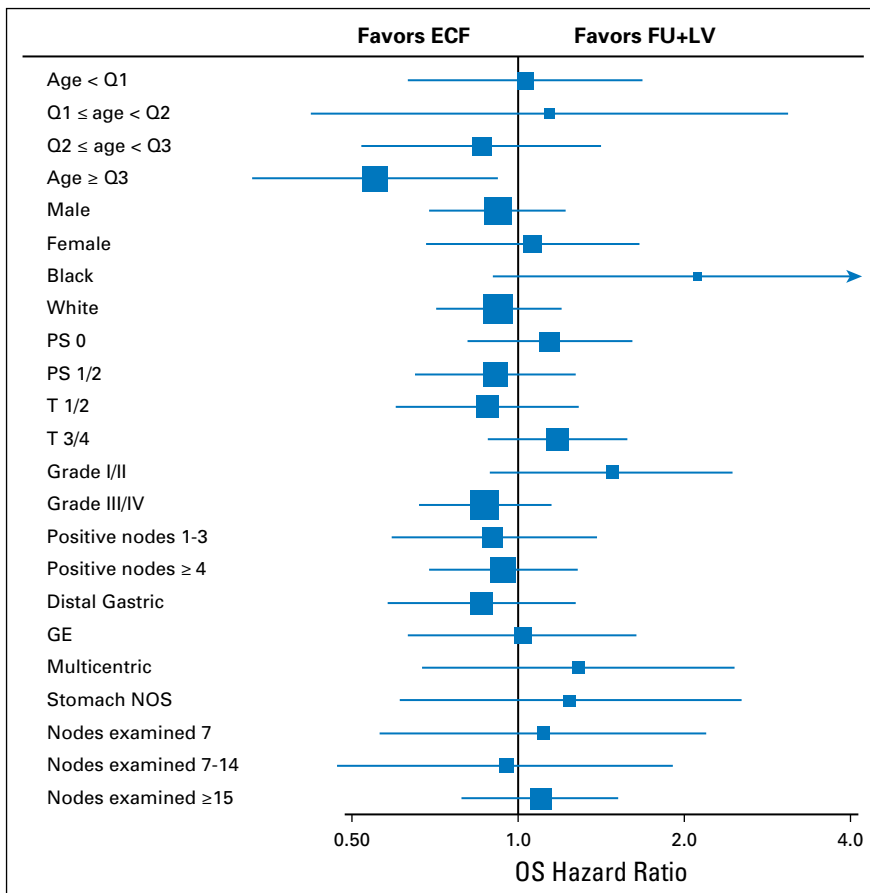
Fig 3. Forest plot of hazard ratios and 95% CIs for overall survival by variable stratum. Numbers of events were too small to estimate the hazard ratios for other race, 0 positive nodes, and proximal gastric primary site. Box size reflects the precision of the estimate, with a larger box size indicating greater precision. ECF, epirubicin, cisplatin, and fluorouracil; FU, fluorouracil; GE, gastroesophageal; LV, leucovorin; NOS, not otherwise specified ; PS, performance status; Q, Quartile.

were higher in the FU plus LV arm, reflecting the toxicity profile of the Mayo Clinic bolus FU plus LV regimen.[15]

We recognized that compliance with protocol-designed radiotherapy planning could also have confounded our results. Our trial included detailed instructions for radiotherapy planning; moreover, the radiation oncology study leaders reviewed all treatment plans before radiotherapy initiation. At central review, 15% of treatment plans were found to contain a major protocol deviation, which were corrected before the start of radiotherapy.

Recent trials have provided additional insight into the role of anthracyclines and radiotherapy in the management of resectable gastroesophageal cancer. In the neoadjuvant therapy of gastroesophageal or esophageal cancer, Combination Chemotherapy in Treating Patients With Esophageal Cancer (MRC OE05) found no survival benefit for the regimen of epirubicin, cisplatin, and capecitabine compared with FU and cisplatin without an anthracycline.[16] In the postoperative management of resected gastric cancer, the ARTIST (Adjuvant Chemoradiation Therapy in Stomach Cancer) trial observed no significant benefit for the addition of radiotherapy to adjuvant capecitabine and cisplatin compared with capecitabine and cisplatin alone.[17] More recently, after neoadjuvant chemotherapy for resectable gastric cancer, the CRITICS (Randomized Phase III Trial of Adjuvant Chemotherapy or Chemoradiotherapy in Resectable Gastric Cancer) trial found that the addition of radiation to postoperative chemotherapy did not improve survival compared with postoperative chemotherapy alone.[18]

Ongoing randomized clinical trials are examining other adjuvant and neoadjuvant treatments in patients with gastric cancer, and we await the results of those studies.[19-21] Beyond those approaches, recent molecular analyses document unique subtypes of gastric cancer that possess distinctive, salient genomic features.[22] Future adjuvant trials will likely leverage these genomic findings to guide targeted approaches for these distinct populations of patients with gastric cancer.

AUTHOR CONTRIBUTIONS

Conception and design: Charles S. Fuchs, Donna Niedzwiecki, Harvey J. Mamon, Joel E. Tepper, Leonard L. Gunderson, Robert J. Mayer
Provision of study materials or patients: Charles S. Fuchs, Harvey J. Mamon, Joel E. Tepper, Richard S. Swanson, Peter C. Enzinger, Daniel G. Haller, Tomislav Dragovich, Steven R. Alberts, Georg A. Bjarnason, Christopher G. Willett, Leonard L. Gunderson, Richard M. Goldberg, Alan P. Venook, David Ilson, Eileen O'Reilly, Kristen Ciombor, David J. Berg, Jeffrey Meyerhardt, Robert J. Mayer

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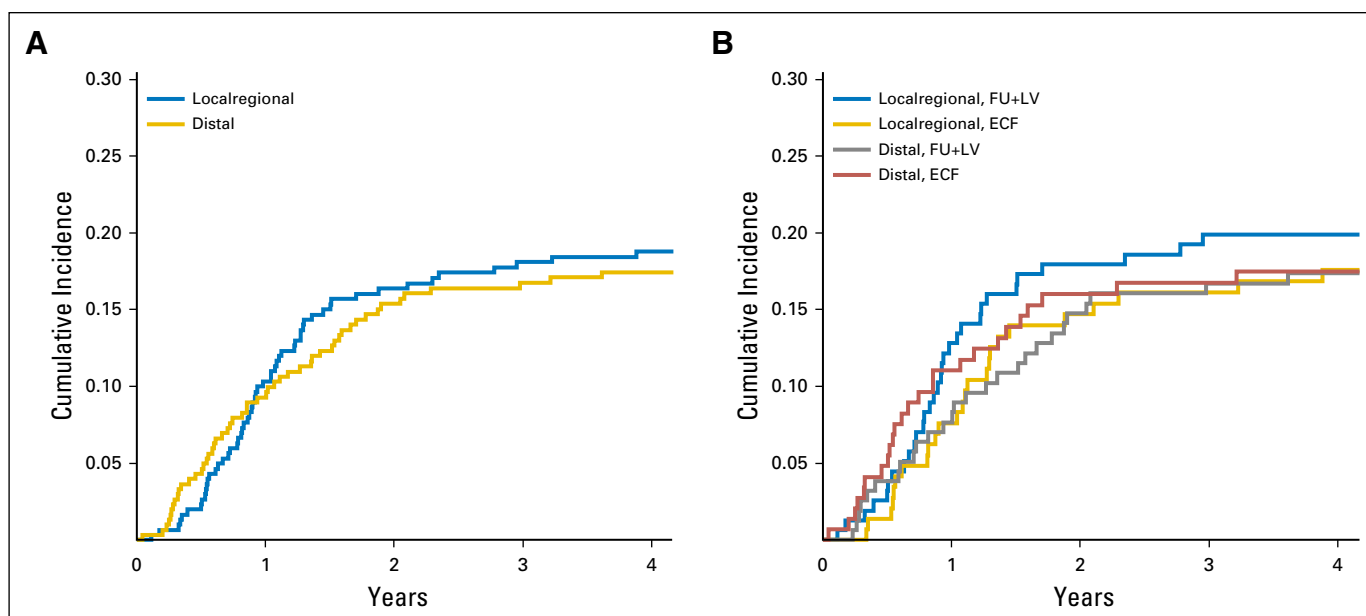**Consulting or Advisory Role:** CASI Pharmaceuticals

Appendix

Fig A1. (A) Cumulative incidence plot for locoregional versus distal recurrence among all patients. Recurrence is measured from study entry until documented recurrence of disease or last follow-up. (B) Cumulative incidence plot for locoregional versus distal recurrence by treatment assignment. Recurrence was measured from study entry until documented recurrence of disease or last follow-up. ECF, epirubicin, cisplatin, and fluorouracil; FU, fluorouracil; LV, leucovorin.

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