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?

C. Kristian Enestvedt, Brian S. Diggs, Donald K. Shipley, Charles R. Thomas, Jr., Kevin G. Billingsley

ABSTRACT

BACKGROUND: The use of adjuvant therapy for resectable gastric adenocarcinoma has become standard of care since the publication of the Intergroup 0116 data. The aims of this study were to (1) assess current practice patterns in gastric cancer treatment, and (2) determine the effect of increasing use of adjuvant chemoradiotherapy on survival in patients with gastric cancer.

PATIENTS AND METHODS: Data from the Oregon State Cancer Registry were abstracted for demographics, disease stage, resection type, number of lymph nodes resected, adjuvant chemoradiotherapy (CRT), and survival for 1996–2006. Patients with stages IB–III disease were divided into cohorts treated through year 2001 (Group 1) or after 2001 (Group 2). Chemoradiotherapy use between groups was compared with the chi-square test. Univariate and multivariate analyses of survival were performed. Binary logistic regression determined predictors for the receipt of CRT.

RESULTS: A total of 308 patients met study criteria. Adjuvant therapy was employed in 17.0% of cases in Group 1 vs. 36.8% in Group 2 ($P < .001$). Tumor stage, tumor location, and American Joint Committee on Cancer (AJCC) stage were independent predictors of survival in both univariate and multivariate analyses. In this retrospective analysis, a modest survival benefit was associated with CRT, but this benefit did not reach statistical significance. Independent predictors for the receipt of CRT included age, AJCC stage, N2 disease, and treatment era.

CONCLUSIONS: While the use of adjuvant CRT increased after publication of Intergroup 0116 data, 63.2% of potentially eligible patients did not receive CRT. Future efforts should focus on identifying and removing barriers to the receipt of adjuvant therapy following resection of gastric adenocarcinoma.

Gastrointest Cancer Res 3:XXX–XXX.

C.K. Enestvedt, MD; B.S. Diggs:
Department of Surgery
Oregon Health and Science University

D.K. Shipley, MS:
Oregon State Cancer Registry

C.R. Thomas, Jr., MD:
Department of Radiation Medicine
Oregon Health and Science University

K.G. Billingsley, MD:
Department of Surgery
Division of Surgical Oncology
Oregon Health and Science University
Portland, OR

This work was presented at the American Society of Clinical Oncology Annual Meeting, June 2008

Submitted: June 10, 2009
Accepted: September 8, 2009

Gastric cancer remains a significant cause of cancer mortality in the United States, with an estimated 22,280 new cases and 11,430 deaths in 2006.[1] Despite efforts by surgeons and medical and radiation oncologists, surgical cure rates remain low and recurrence is common.[2] Five-year survival rates range from 58% to 78% for stage I gastric cancer and the rate is approximately 34% for stage II disease.[3] Clinical research has delineated several treatment-related practices that are critical to optimize outcome in the treatment of gastric cancer patients.[4–9]

Recent randomized controlled trials demonstrate survival benefits for both adjuvant chemotherapy and chemoradiotherapy (CRT).[2,10,11] In 2001, Macdonald and colleagues[2] published the results of the Intergroup 0116 trial (INT116) of adjuvant CRT for gastric cancer. This pivotal trial randomized 556 patients to either surgery alone or to a regimen of 5-fluorouracil/leucovorin (FU/LV) and 45 Gy radiotherapy following surgery. Survival was significantly better in the CRT arm, with a hazard ratio for death of 1.31 (95% confidence interval [CI] 1.08–1.61) for the surgery alone group. Consequently, adjuvant CRT is now considered standard of care after gastrectomy in North America.[12]

Although accurate staging, appropriate lymphadenectomy, and delivery of stage-specific adjuvant treatment are all

Address correspondence to: Kevin G. Billingsley, MD, Chief, Division of Surgical Oncology, Oregon Health & Science University, Mail Code L619, 3181 SW Sam Jackson Park Rd., Portland, OR 97239. Phone: 503-494-5501; Fax: 503-494-7573

measures that have been shown to offer survival benefits to gastric cancer patients, few data are available about the implementation of these processes in actual clinical practice. Likewise, few population-based studies examine the use of these techniques. The central aim of this study was to determine the extent of change in the patterns of CRT use since publication of INT116. Secondary aims were (1) to determine the survival benefit associated with the use of adjuvant CRT in a population-based cohort, and (2) to identify patients who may have been eligible for CRT but did not receive therapy. This report provides a comprehensive picture of current patterns of care regarding the use of adjuvant therapy for resected gastric cancer and forms the basis for future efforts at quality improvement in the treatment of gastric cancer.

PATIENTS AND METHODS

Data from the Oregon State Cancer Registry (OSCaR) were abstracted for the years 1996 through 2006. The registry includes all cases of cancer in the state, including records from 27 hospitals. All patients with surgically treated gastric cancer were identified using International Classification of Diseases, 9th Version (ICD-9) diagnosis codes, Current Procedure Terminology (CPT) codes, and the 2004 Surveillance, Epidemiology and End Results (SEER) Program Coding and Staging Manual.[13–15] Data for all patients with potentially resectable disease were collected (N = 951) and from this group, those who underwent a resection — either endoscopic or surgical — were selected (n = 644). Finally, only those patients with stages IB–III, with adenocarcinoma or signet ring cell histologic subtype, and who underwent surgical resection were included. The dataset used in this analysis matched on a stage-specific basis to the patients chosen for the INT116 study. Data were abstracted for age, gender, date of death, date of surgery, tumor histology, number of nodes resected, American Joint Committee on Cancer (AJCC Cancer Staging Manual Version 6) TNM stage, type of resection, tumor location, reason for not receiving CRT, and vital status.[16]

To evaluate the change in treatment after publication of the INT116 data, all patients who underwent surgery through 2001 were assigned to Group 1, and those who underwent resection after 2001 were assigned to Group 2. We chose the year 2001 as the transition period to measure the change in use of CRT because this was the year INT116 data were published. Analyses of lymph nodes resected and use of adjuvant CRT was performed to compare Groups 1 and 2 using the Mann-Whitney U test and the chi-square test, respectively.

Kaplan-Meier survival curves were plotted and univariate survival analysis was performed using the log-rank test for each of these subgroups. Multivariate analysis was performed to determine the influence of age, gender, AJCC stage, histology, nodal status, T stage, resection type, adjuvant CRT, tumor location, and treatment period on survival using the Cox proportional hazards model. Binary regression analysis was performed on the same variables to determine predictors for receipt of CRT. The linked variables AJCC stage and T and N stage were included in separate models, with AJCC stage used as the primary variable for both regression analysis and survival. Survival advantage was reported as hazard ratio with 95% confidence interval.

The SPSS software package version 15.0 (SPSS Inc, Chicago) was used for statistical analyses. Parametric and nonparametric tests were used where appropriate, depending on the distribution of the data. Significance was reported for a P value $< .05$. All personal identifying data were removed from the dataset in accordance with OSCaR and Health Insurance Portability and Accountability Act (HIPAA) regulations. This study was approved by the Institutional Review Board at our institution.

RESULTS

Demographics

A total of 308 patients met study criteria. Overall, the median age was 72 years (range, 27–98). Fifty-nine percent of the patients were men. Twenty-one percent of tumors were signet ring subtype and the remainder (78.9%) were adenocarcinoma. The most frequent T stage was T3 (43.2%), and patients most often had N1 disease (40.9%). By AJCC stage, more patients presented with stage III disease, followed by stages II and IB (47.1%, 30.5%, and 22.4% respectively). The majority of tumors were isolated to the stomach (86.4%), with a minority involving the gastroesophageal junction (13.6%). Most patients had a subtotal gastrectomy (66.9%). A majority of patients were treated in the first study period (through 2001), and these 194 patients comprised 63% of the cohort.

Demographic data comparing patients who received CRT to those who did not are presented in Table 1. A significant difference in age was observed — the median age in the group that received CRT was 64 years vs. 75 years in the non-CRT group ($P < .001$). Patients who received CRT were more likely to be node positive (70.7%) compared to those who did not (55.3%, $P = .043$) and were also more likely to have a higher AJCC stage ($P = .014$). A larger percentage of those who received CRT had tumors that involved the stomach and gastroesophageal junction than did those who did not (21.3% vs. 11.2%, $P = .033$). No significant differences in gender, T stage, tumor histology, and type of resection were noted between the two groups.

Chemoradiotherapy and Treatment Period

A significant increase in the use of adjuvant CRT was observed between the two study periods. Through the year 2001, CRT was employed in less than one fifth of patients, whereas CRT was administered more than twice as frequently after 2001 (17.0 vs. 36.8%, $P < .001$, Table 1). The change in CRT usage over time is depicted in Figure 1. Binary logistic regression identified age, AJCC stage, and treatment period as independent predictors for receipt of CRT (Figure 2). Older patients were less likely to receive therapy (odds ratio [OR] 0.924, 95% CI 0.899–0.949, $P < .001$). Patients with AJCC stage II disease and stage III disease were 3.98 times (95% CI 1.47–10.82, $P = .007$) and 3.17 times (95% CI 1.20–8.39, $P = .02$), respectively, more likely to receive CRT than patients with stage IB disease. Patients treated after 2001 were 4.3 times more likely to receive adjuvant therapy (95% CI 2.19–8.40, $P < .001$). Variables that had no apparent effect on use of CRT

Table 1. Demographic and tumor features based on receipt of chemoradiotherapy (CRT) for 308 patients with resected gastric cancer

	CRT (%)	No CRT (%)	*P* value*
Median age in years (range)	64.0 (34–83)	75.0 (27–98)	< .001†
Number male	47 (62.7)	134 (57.5)	.501
AJCC Stage			.014
IB	8 (10.7)	61 (26.2)	
II	29 (38.7)	65 (27.9)	
III	38 (50.7)	107 (45.9)	
T Stage			.493
1	1 (1.3)	9 (3.9)	
2	17 (22.7)	74 (31.8)	
3	34 (45.3)	99 (42.5)	
4	5 (6.7)	16 (6.9)	
Unknown	18 (24.0)	35 (15.0)	
N Stage			.043
0	17 (22.7)	89 (38.2)	
1	36 (48.0)	90 (38.6)	
2	17 (22.7)	39 (16.7)	
Unknown	5 (6.7)	15 (6.4)	
Tumor location			.033
Stomach only	59 (78.7)	207 (88.8)	
Stomach and GEJ	16 (21.3)	26 (11.2)	
Resection			.751
Subtotal	53 (70.7)	153 (65.7)	
Total or radical	16 (21.3)	52 (22.3)	
Unknown	6 (8.0)	28 (12.0)	
Histology			.194
Adenocarcinoma	55 (73.3)	188 (80.1)	
Signet ring	20 (26.7)	45 (19.3)	
Treatment period			< .001
Through 2001 (Group 1)	33 (17.0)	161 (83.0)	
After 2001 (Group 2)	42 (36.8)	72 (63.2)	
Totals	75	233	

*All *P* values by chi-square except median patient age
† *P* value by Mann-Whitney U
Abbreviation: AJCC = American Joint Committee on Cancer; CRT = chemoradiotherapy; GEJ = gastroesophageal junction

Table 2. Breakdown of patients by treatment era and reasons for not receiving chemoradiotherapy (CRT)

	Through 2001	After 2001	Total
CRT not administered	161 (83.0)	72 (63.2)	233 (75.6)
Reason			
Not part of treatment plan	99 (51.0)	58 (50.9)	157 (51)
Contraindicated	2 (1.0)	3 (2.6)	5 (1.6)
Single modality only	2 (1.0)	2 (1.8)	4 (1.3)
Recommended, not received	42 (21.6)	2 (1.8)	45 (14.6)
Recommended, refused	3 (1.5)	6 (5.3)	9 (2.9)
Unknown	13 (6.7)	1 (0.9)	14 (4.5)
CRT administered	33 (17.0)	42 (36.8)	75 (24.4)
Totals	194	114	308

included gender, T stage, N stage, tumor location, and resection type. However, on subset analysis, patients with between 7 and 15 positive nodes (N2) were 3.5 times more likely to receive CRT (95% CI 1.13–10.58, $P = .030$).

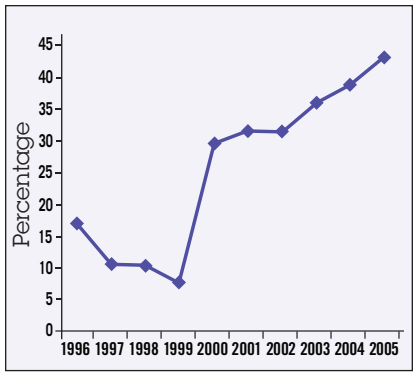

Figure 1. Percentage of patients who received adjuvant CRT by year of surgical treatment.

When we examined the reasons reported for not administering CRT the most frequent explanation was "not planned," as indicated in 51% of cases (n = 157, Table 2). Only five patients (1.6%) were not offered CRT due to contraindications attributed to other comorbid conditions or surgical complications. Four patients (1.3%) received only one modality (ie, either chemotherapy or radiotherapy but not both). In 45 patients (14.6%), CRT was recommended but not delivered for unspecified reasons. Nine patients refused CRT (2.9%). In 14 potentially eligible patients (4.5%) CRT was not given, but it is unknown whether it was recommended.

Overall and Subset Survival

Median survival for the entire cohort was 10 months (range 0–125 months). Patients with stage IB disease had a median survival of 30 months, those with stage II survived a median of 22 months, and the median survival for stage III was 13 months ($P < .001$, log rank, Figure 3).

The best predictors of survival were AJCC stage, T stage, and tumor location (Table 3). AJCC stage significantly correlated with survival in both univariate and multivariate models ($P < .001$), as did T stage ($P = .031$ and $P = .011$, respectively). Those patients with AJCC stages II and III were, respectively, 1.38 and 2.39 times more likely to die than those with stage I disease. With each increase in T stage the hazard ratio for death likewise increased incrementally from 2.67 for T2 lesions to 4.67 for T4 lesions when compared to T1 lesions. The N stage approached significance in univariate analysis ($P = .056$) and

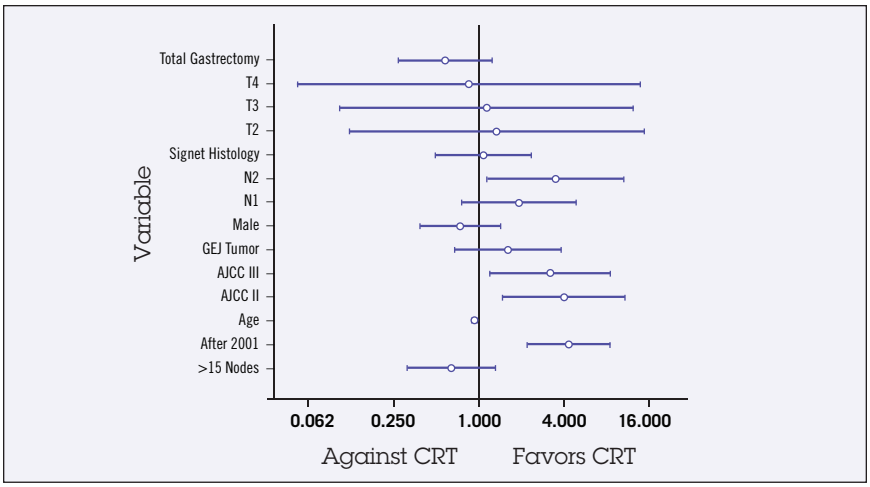

Figure 2. Predictors for receipt of CRT based on binary regression modeling.

Table 3. Univariate and multivariate survival analysis for 308 patients with resectable gastric adenocarcinoma

Category	Median survival (months)	*P* value Univariate	*P* value Multivariate	Hazard ratio (95% CI)
AJCC stage		< .001	< .001	
Ib	30		NA	Reference
II	22		.175	1.38 (0.87–2.20)
III	13		< .001	2.39 (1.56–3.68)
T stage		.031	.011	
T1	47		NA	Reference
T2	23		.068	2.67 (0.93–7.67)
T3	13		.012	3.80 (1.34–10.77)
T4	16		.010	4.67 (1.45–15.00)
N stage		.056	.020	
N0	22		NA	Reference
N1	16		.008	1.64 (1.14–2.37)
N2	13		.038	1.59 (1.03–2.45)
≥ 15 nodes sampled		.942	.738	
No	17			Reference
Yes	17			0.94 (0.67–1.33)
CRT		.267	.051	
No	15			Reference
Yes	20			0.67 (0.44–1.00)
Type resection		.038	.302	
Subtotal	20			Reference
Total	13			1.20 (0.85–1.71)
Tumor location		.009	.009	
Stomach only	19			Reference
Stomach + GEJ	12			1.75 (1.15–2.66)

Abbreviations: AJCC = American Joint Committee on Cancer; CI = confidence interval; CRT = chemoradiotherapy; GEJ = gastroesophageal junction

Table 4. Number of lymph nodes sampled stratified according to American Joint Committee on Cancer (AJCC) stage.

AJCC Stage	< 15 lymph nodes (%)	≥ 15 lymph nodes (%)	Total
IB	51 (73.9)	18 (26.1)	69
II	66 (70.2)	28 (29.8)	94
III	92 (63.4)	53 (36.6)	145
Total	209 (67.9)	99 (32.1)	308

was a statistically significant predictor of survival on multivariate analysis ($P = .020$). Median survival decreased stepwise for each increase in N stage. For both univariate and multivariate analysis, 15 or more nodes identified in the surgical specimen and the use of CRT did not significantly affect survival. However, a trend toward improved survival was noted among patients who received CRT. In patients who had adjuvant CRT the median survival was 20 months compared to 15 for those who did not, with an HR for death of 0.71 (95% CI 0.48–.07; $P = .267$ univariate, $P = .051$ multivariate).

Number of Nodes Resected

For all years, the median number of lymph nodes sampled was 10 (interquartile range 6–17). Overall, 32.1% of all patients had at least 15 nodes sampled (Table 4). There was a significant difference in the number of nodes sampled across all years ($P = .037$, Kruskal-Wallis test). Significantly more lymph nodes were sampled with total gastrectomies than when subtotal resections were performed ($P = .002$). Also, those patients who had a subtotal gastrectomy were less likely to have 15 nodes sampled than those with a total or radical gastrectomy (28.4% vs. 45.1%, $P = .013$).

DISCUSSION

In this study, we have shown a significant increase in the use of adjuvant CRT following resection for gastric cancer since publication of the INT116 trial results in 2001. The later treatment era was an independent predictor of the receipt of CRT, indicating a significant change in practice patterns. However, 63% of patients with

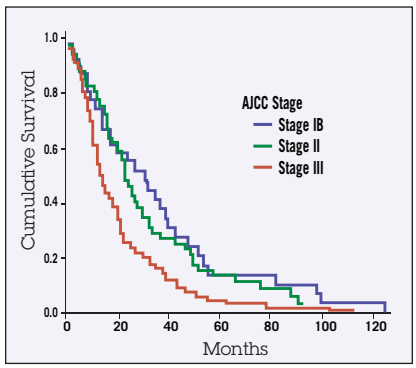

Figure 3. Kaplan-Meier survival according to American Joint Committee on Cancer (AJCC) stage ($P < .001$, log rank).

resected gastric cancer did not receive adjuvant chemoradiotherapy after the release of the relevant clinical trial results. Our results are similar to those of Coburn et al,[17] who demonstrated that the percentage of patients who received adjuvant radiotherapy after INT116 publication increased from 14.6% to 30.4%. The most significant predictor of receipt of adjuvant CRT was patient age. In the current study, patients who received adjuvant therapy were substantially younger (median age 64 vs. 75) than patients who did not. In addition, patients with more advanced stage and extensive lymph node involvement were more likely to receive adjuvant therapy.

Selection bias for the receipt of CRT against those with advanced age may indicate decreased performance status, comorbid conditions, or postoperative complications that might have precluded the delivery of CRT to this group. When we examined the reasons reported for "no CRT," these patients were more likely to be older and were more likely to have earlier-stage disease in accordance with both N and AJCC staging. On binary regression analysis, the subset of patients stage N2 was 3.5 times more likely to receive CRT than other nodal groups. In effect, younger patients with more advanced disease were more likely to receive CRT than older patients with early-stage cancer.

Other investigators have found marked age-related variability in the application of adjuvant therapy for a variety of malignancies. Studies of adjuvant treatment for colon cancer have demonstrated a large disparity in patterns administration, with patients over 70 receiving adjuvant therapy at a fraction of the frequency of their younger counterparts. Using state cancer registry data from California, Ayanian and colleagues[18] reported that adjuvant therapy for stage-appropriate colon cancer is provided to 88% of patients younger than 55 years but to only 47% of patients over 75. A similar pattern favoring the use of adjuvant therapy in younger patients has been reported in a patterns of care audit from a large community cancer center.[19]

Despite these results, there is no indication that elderly patients, at least those with colorectal cancer, benefit any less from CRT than their younger cohorts. A pooled analysis of three large clinical trials of adjuvant treatment for colorectal cancer demonstrate that elderly patients derive survival benefit from adjuvant therapy in the same proportion as do younger patients.[20] A comparable analysis has not been performed in patients receiving adjuvant therapy for gastric cancer. There is little doubt that patients must be carefully selected for adjuvant therapy following gastrectomy, but the findings of this study suggest that some patients, particularly elderly individuals, are not receiving stage-appropriate adjuvant treatment that would likely improve their chance of extended survival.

One of the limitations of the current study is that the data were not detailed enough to define comorbid conditions that precluded the delivery of adjuvant therapy for certain patients. It is possible that many patients did not have specific comorbidities, but appeared frail and were not perceived as good candidates for adjuvant therapy. These patients may be represented in the 14.6% who did not receive CRT for "unspecified reasons." The addition of ASA (American Society of Anethesiologists) class or Charlson comorbidity index to the dataset for future studies might help clarify this issue.[21]

While a greater proportion of patients received CRT after 2001, the continued high percentage of patients in Group 2 whose treatment plan did not include CRT could indicate that INT116 results have not been thoroughly disseminated to the oncology community. Additionally, gaps may exist between surgeons, medical and radiation oncologists, and primary care physicians in directing patients to the appropriate therapies. While we did not track specific referral patterns in this study, exploring the link between multidisciplinary treatment teams and use of adjuvant CRT in gastric cancer patients may also prove important for future studies.

In this study, median survival for patients who received CRT postoperatively was 20 months for all stages (IB-III). In the Intergroup study, overall median survival was 36 months. For those who did not receive CRT, the median survival was 15 months in this study vs. 27 months for those patients in INT116. There are several possible explanations for the disparity in outcomes between the clinical trial setting and actual clinical practice as observed by this study. First, our investigation included all patients with resected gastric cancer, irrespective of margin status. Undoubtedly, patients with margin-positive resections (R1) were represented in our dataset. The INT116 study excluded patients with pathologically positive margins, and a margin-free (R0) resection on pathologic examination was a requisite for study inclusion.[2] It has been well established that an R0 resection significantly improves survival.[22] Margin positivity in our study likely had a strong negative influence on patient survival, despite CRT. Second, other differences in patient selection between the study populations may have substantially contributed to the disparity in outcomes. INT116 used the 1988 AJCC staging criteria including patients with stage IB-IVM0 disease. This staging system used different criteria to determine N stage, while the current AJCC uses newer categories (1–6, 7–15, >15 nodes) to define N stage. This makes comparison of the number of patients in each stage grouping challenging. It is likely that discrepancies in staging between the two sets of patients results in understaging of patients that were treated off the structured staging program inherent in a clinical trial.

Chemoradiotherapy remains a difficult ordeal for patients. Even within the framework of INT116, only 64% of patients treated with chemoradiotherapy received the entire course of therapy. As such, it is possible that the outcomes reported in the current study reflect the difficulties of administering a full adjuvant course of chemoradiotherapy to gastric cancer patients, all of whom are still recovering from complex gastrointestinal surgery. It is also important to note that patients were analyzed based on receipt of any regimen of CRT rather than strict adherence to the INT116 protocol. In addition, technical challenges exist related to radiation treatment planning for gastric cancer that may not be widely appreciated in general practice. During the course of the Intergroup study, a significant proportion of study patients required modification of the submitted treatment plans because of planned overtreatment, undertreatment, or inclusion of critical structures within the radiation treatment field.[2] Data in the current study were

not sufficiently detailed to measure the proportion of patients completing therapy, nor did they supply specific details about radiation treatment or chemotherapy programs. It is clear, however, that quality issues related to adjuvant treatment for gastric cancer should be a research priority in future studies.

We have seen an encouraging increase in the use of adjuvant CRT for patients following resection for gastric cancer since 2001. It appears, however, that adjuvant CRT was not considered in the initial treatment plans of a large percentage of patients. Further investigations should focus on factors that contribute to the undertreatment of groups of potentially eligible patients (ie, older, earlier stage). Studies should explore which specific indicators or contraindications limited the receipt of CRT and if additional health system factors such as geographic limitations or socioeconomic factors play a role. Finally, future efforts aimed at physician education for both appropriate surgical and medical therapy for gastric cancer will be essential to ensure that patients are being adequately staged and subsequently receive stage-appropriate therapy.

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Disclosures of Potential Conflicts of Interest
The authors indicated no potential conflicts of interest.