Chemoradiation Improves Survival Compared With Chemotherapy Alone in Unresected Nonmetastatic Gastric Cancer

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Abstract

Background: Limited data are available to guide management of patients with stage I–III gastric cancer not undergoing potentially curative surgical resection. We compared survival outcomes associated with chemotherapy alone versus chemoradiation (CRT) in the treatment of nonmetastatic gastric cancer. **Methods:** Patients with gastric adenocarcinoma from 2004 to 2015 were identified using the National Cancer Database. Patients were excluded if they had surgery, metastatic disease, or T0, Tis, or T1a disease. Logistic regression was used to evaluate predictors of CRT use. Cox proportional hazards modeling was performed to compare overall survival (OS) between chemotherapy alone and CRT in overall and propensity score–matched cohorts. **Results:** We identified 4,795 patients with stage I–III gastric adenocarcinoma who did not undergo surgery, at a median follow-up of 11.8 months. A total of 3,316 patients (69.2%) received chemotherapy alone and 1,479 patients (30.8%) received CRT. Predictors of increased CRT use were age ≥ 65 years (odds ratio [OR] 1.68; 95% CI, 1.43–1.99; $P < .001$), Charlson-Deyo comorbidity score ≥ 2 (OR, 1.46; 95% CI, 1.18–1.81), and treatment at a community facility (OR, 1.27; 95% CI, 1.07–1.51; $P = .006$). Patients receiving CRT had a 2-year OS rate of 28.3% compared with 21.5% among those receiving chemotherapy. Multivariate analysis showed that CRT was associated with improved OS (hazard ratio [HR], 0.82; 95% CI, 0.77–0.89; $P < .001$). After propensity score matching, a persistent survival benefit was observed (HR, 0.80; 95% CI, 0.74–0.88; $P < .001$). **Conclusions:** In patients with stage I–III gastric cancer not undergoing surgical resection, CRT was associated with improved survival compared with chemotherapy alone. However, only 30.8% of patients received CRT in this setting.

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Gastric cancer is the fifth most common cancer and the third leading cause of cancer mortality globally, with an estimated 28,000 newly diagnosed cases in the United States in 2017.^{1,2} Surgical resection, including gastrectomy and lymph node dissection, has been established as the primary curative treatment modality for locally advanced gastric cancer.^{3,4} Perioperative chemotherapy, adjuvant chemotherapy, or adjuvant chemoradiation (CRT) are given in conjunction with surgery based on data from phase III trials.^{5–9}

However, $>30\%$ of patients with stage I–III gastric and gastroesophageal cancer in the United States do not undergo surgical resection.^{10,11} Reasons for non-surgical management of these patients may include anatomic unresectability, medical inoperability due to comorbidities, limited access to specialized surgical care, or patient choice.^{12,13} The optimal management of patients who do not receive curative resection for nonmetastatic gastric cancer is unclear. Consensus treatment guidelines have divergent recommendations

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in this setting. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Gastric Cancer recommend consideration of CRT versus palliative management (potentially involving chemotherapy alone depending on performance status),¹⁴ whereas ESMO and Japanese Gastric Cancer Association (JGCA) guidelines recommend palliative chemotherapy.^{15,16}

Early trials in gastric cancer by the Gastrointestinal Tumor Study Group (GITSG) and Mayo Clinic showed poor survival outcomes with CRT in the absence of curative surgery, although patients receiving CRT in these studies experienced significant treatment toxicity.^{17–19} Both chemotherapy and radiation therapy (RT) techniques have advanced significantly since the completion of these trials. More recent phase II trials showed favorable outcomes with combined CRT, but these are single-arm studies.^{20,21} No contemporary studies, either randomized or retrospective, have compared chemotherapy versus CRT in patients with unresected nonmetastatic gastric cancer.

Given the lack of data addressing management in this setting, we used the National Cancer Database (NCDB) to compare survival outcomes for chemotherapy alone versus CRT in patients with stage I–III gastric cancer, focusing on patients who did not undergo surgical resection.

Methods

The NCDB is a national oncology database sponsored by the American College of Surgeons and the American Cancer Society. It includes patient data from >1,500 accredited facilities and captures >70% of newly diagnosed cancer cases in the United States.²² The data used in the study are derived from a deidentified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used, or the conclusions drawn from these data by the investigators.

Patient Cohort Definition

Using the NCDB, a total of 121,290 patients were identified with gastric cancer diagnosed from 2004 to 2015. Patients were excluded if they had histology other than adenocarcinoma, had metastatic disease or unknown metastatic status at presentation, tu-

mors with primary site in the gastroesophageal junction, or underwent any surgery of the primary site (including gastrectomy, local tumor destruction, or local excision). Additional exclusions included patients with stage T0, Tis, or T1a disease and those who did not receive any chemotherapy. These criteria are summarized in Figure 1. The final cohort of 4,795 patients was stratified into those receiving CRT (n=1,479) and those receiving chemotherapy alone (n=3,316). These groups were compared on the primary end point of overall survival (OS).

Variable Definitions

All variables were selected a priori. Demographic variables including age, year of diagnosis, race, insurance status, facility type, and facility location were defined according to their respective data fields in the NCDB data dictionary.²³ Race was categorized as non-Hispanic white, black, or other (including Hispanic, Asian, and other). Facility regions were grouped into Northeast, South, Midwest, and West regions. Insurance status was grouped into government (Medicare/Medicaid/other), private, or uninsured. Facility volume was calculated within the

Figure 1. CONSORT diagram illustrating case selection for final patient cohort. Abbreviations: chemo, chemotherapy; CRT, chemoradiation; NCDB, National Cancer Database; RT, radiation therapy.

subset of patients with gastric cancer receiving no surgery, and divided into tertiles by volume (low, medium, high).

For pathologic factors, the T and N stages were defined by the clinical T and N stage fields, respectively. In cases where a biopsy was performed and a pathologic T or N stage was recorded, these were used. AJCC stage group was recorded based on the corresponding field; when missing, the stage group was classified based on the T and N staging. Histology of adenocarcinoma was defined using ICD for Oncology, 3rd edition (ICD-O-3) codes, including codes 8140–8145, 8200–8220, 8255–8263, 8320–8384, 8400–8490, and 8550–8574.²⁴

For treatment variables, receipt of chemotherapy and RT were defined by their respective fields in the data dictionary. Sequencing of treatment was determined according to the time between diagnosis and initiating that modality of treatment. Concurrent CRT was defined as initiation of chemotherapy and RT no more than 14 days apart; otherwise, CRT was classified as sequential.

Statistical Analysis

Descriptive statistics for each of the demographic, pathologic, and treatment variables were calculated. OS was plotted using the Kaplan-Meier method with differences across groups assessed using the log-rank statistic. Survival time was calculated from date of diagnosis until date of death or last contact if alive. Patients alive at end of follow-up were censored at last contact date.

Survival analyses were performed using the log-rank test for univariate analysis and Cox proportional hazards regression for multivariate analysis to estimate hazard ratios (HRs). The final parsimonious multivariate Cox model was formed by using hierarchical backwards selection of variables significant at $P < .10$. The proportional hazards assumption was assessed for all variables in the final multivariate analysis and was not violated.²⁵

A multivariate logistic regression was performed to assess factors predictive of receiving CRT. This was also used to generate propensity scores, with all factors included in propensity score generation regardless of statistical significance—with the exception of AJCC stage grouping, which was omitted due to collinearity with T and N staging. We specified

a subset analysis a priori to compare HR by AJCC overall stage.

Propensity score-matched (PSM) analysis was performed to compare outcomes for patients receiving CRT to chemotherapy alone. One-to-one nearest neighbor matching without replacement was performed for patients with complete follow-up to form the final propensity-matched cohort, with caliper width of 0.10. To further support the assumption of balance between groups, the propensity score was stratified into quintiles and a standardized difference between the treatment groups of <0.10 was validated. Cox proportional hazards regression was performed for survival analysis in the final matched cohort. Conditional landmark analyses using 3- and 6-month landmarks were used to mitigate guarantee-time bias.

All statistical analyses were performed using the open-source R statistical environment (version 3.4.2; R Core Team 2017) and SPSS statistical software (version 23.0; IBM Corporation).

Results

Patient Cohort Characteristics

A total of 4,795 patients at a median follow-up of 11.8 months were identified in the NCDB that met the inclusion criteria (Figure 1). Demographic, pathologic, and treatment characteristics of our patient cohort are summarized in Table 1. Most patients were aged ≥ 65 years (59.2%), non-Hispanic white (55.9%), and had government insurance (ie, Medicare, Medicaid, other; 60.5%).

When stratified by treatment received, 3,316 patients (69.2%) received chemotherapy alone and 1,479 patients (30.8%) received CRT. Among the 1,479 patients who received CRT, 947 (64.0%) received concurrent CRT and 524 (35.4%) received sequential treatment; 8 patients had unknown sequence. No significant difference in survival was seen between those receiving sequential and concurrent treatment. Median time from diagnosis to start of RT was 63 days (interquartile range [IQR], 31–91 days). For those who underwent sequential treatment, median time from start of chemotherapy to start of RT was 64 days (IQR, 22–111 days) and median RT dose among patients receiving CRT was 45 Gy (IQR, 43.2–50.4 Gy). A total of 536 patients (36.2%) received doses <45 Gy; these patients had a median

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Table 1. Baseline Patient Characteristics (N=4,795)

Baseline Characteristics	n (%)
Sociodemographic factors	
Year of diagnosis	
2004–2006	921 (19.2)
2007–2009	1,161 (24.2)
2010–2012	1,229 (25.6)
2013–2015	1,484 (30.9)
Age, y	
<65	1,956 (40.8)
≥65	2,839 (59.2)
Charlson-Deyo comorbidity score	
0	3,465 (72.3)
1	915 (19.1)
≥2	415 (8.7)
Facility region	
Northeast	1,101 (23.0)
South	1,804 (37.6)
Midwest	957 (20.0)
West	738 (15.4)
Unknown	195 (4.1)
Race	
Non-Hispanic white	2,682 (55.9)
Black	998 (20.8)
Other	1,082 (22.6)
Unknown	33 (0.7)
Insurance status	
Government	2,903 (60.5)
Private	1,399 (29.2)
Uninsured	246 (5.1)
Unknown	247 (5.2)
Facility volume, tertile	
Lowest	519 (10.8)
Middle	974 (20.3)
Highest	3,302 (68.9)
Facility type	
Academic/Research	2,394 (49.9)
Community/Comprehensive community	2,206 (46.0)
Unknown	195 (4.1)
Pathologic factors	
Anatomic location	
NOS	1,968 (41.0)
Antrum	1,009 (21.0)
Body	661 (13.8)
Fundus	366 (7.6)
Pylorus	139 (2.9)
Lesser curvature NOS	450 (9.4)
Greater curvature NOS	202 (4.2)
T stage	
T1	490 (10.2)
T2	606 (12.6)
T3	1,341 (28.0)
T4	911 (19.0)
Unknown	1,447 (30.2)
N stage	
N0	1,857 (38.7)
N1	1,279 (26.7)
N2	398 (8.3)
N3	129 (2.7)
Unknown	1,132 (23.6)
AJCC stage group	
I	798 (16.6)
II	1,128 (23.5)
III	1,389 (29.0)
Unknown	1,480 (30.9)
Treatment factors	
Treatment received	
Chemotherapy alone	3,316 (69.2)
CRT	1,479 (30.8)

Abbreviations: CRT, chemoradiation; NOS, not otherwise specified.

survival of 9 months compared with 14.3 months in those receiving ≥45 Gy (log-rank $P<.001$).

CRT Use

Table 2 illustrates the distribution of factors between the CRT group and the chemotherapy-alone group, in addition to odds ratios (ORs) for receipt of CRT. We identified several factors that were predictive of increased CRT use, including age ≥65 years (OR, 1.68; 95% CI, 1.43–1.99; $P<.001$), Charlson-Deyo comorbidity score ≥2 (OR, 1.46; 95% CI, 1.18–1.81; $P<.001$), treatment at community facility rather than academic (OR, 1.27; 95% CI, 1.07–1.51; $P=.006$), and T2 disease compared with the reference group of T1 (OR, 1.44; 95% CI, 1.12–1.85; $P=.005$). Factors associated with decreased CRT use were race other than non-Hispanic white or black (OR, 0.76; 95% CI, 0.64–0.90; $P=.002$), year of diagnosis after 2006 ($P<.001$), private insurance versus government insurance (OR, 0.85; 95% CI, 0.73–0.98; $P=.024$), and treatment at a facility with volume in the highest tertile (OR, 0.81; 95% CI, 0.69–0.94; $P=.007$).

Survival Analysis

Patients receiving chemotherapy alone had a median survival of 11.3 months and a 2-year OS rate of 21.5%, whereas those receiving CRT had a median survival of 12.3 months and a 2-year OS rate of 28.3% (log-rank $P<.001$). Kaplan-Meier curves comparing chemotherapy alone and CRT are depicted in Figure 2A.

The results of multivariate survival analysis are summarized in Table 3. Significant predictors of improved OS included later year of diagnosis, Charlson-Deyo comorbidity score of 0, nonwhite race, treatment at an academic facility, T stage <T4, treatment in the Northeast region, and receipt of CRT. After multivariate adjustment, receipt of CRT continued to be significantly associated with improved OS (HR, 0.82; 95% CI, 0.77–0.89; $P<.001$). On subset analysis, a survival benefit for CRT was observed in 798 patients with AJCC stage I gastric cancer (HR, 0.72; 95% CI, 0.60–0.86; $P<.001$) and 1,128 with AJCC stage II disease (HR, 0.81; 95% CI, 0.68–0.95; $P=.009$). There was a trend toward improvement with CRT but no statistically significant difference in survival between CRT and chemotherapy alone

Table 2. Comparative Use of CRT by Baseline Characteristics

	Chemotherapy (n=3,316)	CRT (n=1,479)	OR	95% CI	P Value
Sociodemographic factors					
Year of diagnosis					
2004–2006	614 (66.7%)	307 (33.3%)	1	Ref	
2007–2009	839 (72.3%)	322 (27.7%)	0.67	0.55–0.82	<.001*
2010–2012	836 (68.0%)	393 (32.0%)	0.68	0.56–0.82	<.001*
2013–2015	1,027 (69.2%)	457 (30.8%)	0.61	0.50–0.74	<.001*
Age, y					
<65	1,515 (77.5%)	441 (22.5%)	1	Ref	
≥65	1,801 (63.4%)	1,038 (36.6%)	1.68	1.43–1.99	<.001*
Charlson-Deyo comorbidity score					
0	2,443 (70.5%)	1,022 (29.5%)	1	Ref	
1	629 (68.7%)	286 (31.3%)	1.01	0.86–1.19	.905
≥2	244 (58.8%)	171 (41.2%)	1.46	1.18–1.81	.001*
Facility region					
Northeast	788 (71.6%)	313 (28.4%)	1	Ref	
South	1,217 (67.5%)	587 (32.5%)	1.22	1.03–1.45	.021*
Midwest	624 (65.2%)	333 (34.8%)	1.28	1.05–1.56	.012*
West	521 (70.6%)	217 (29.4%)	1.20	0.97–1.49	.088
Unknown	166 (85.1%)	29 (14.9%)	1.30	NA	
Race					
Non-Hispanic white	1,793 (66.9%)	889 (33.1%)	1	Ref	
Black	677 (67.8%)	321 (32.2%)	1.06	0.90–1.25	.490
Other	819 (75.7%)	263 (24.3%)	0.76	0.64–0.90	.002*
Unknown	27 (81.8%)	6 (18.2%)	0.62	0.25–1.53	.298
Insurance status					
Government	1,909 (65.8%)	994 (34.2%)	1	Ref	
Private	1,068 (76.3%)	331 (23.7%)	0.85	0.73–0.98	.024*
Uninsured	193 (78.5%)	53 (21.5%)	0.94	NA	
Unknown	146 (59.1%)	101 (40.9%)	1.78	NA	
Facility volume, tertile					
Lowest	328 (63.2%)	191 (36.8%)	1	Ref	
Middle	644 (66.1%)	330 (33.9%)	0.90	0.76–1.07	.241
Highest	2,344 (71.0%)	958 (29.0%)	0.81	0.69–0.94	.007*
Facility type					
Academic/Research	1,711 (71.5%)	683 (28.5%)	1	Ref	
Community/Comprehensive community	1,439 (65.2%)	767 (34.8%)	1.27	1.07–1.51	.006*
Unknown	166 (85.1%)	29 (14.9%)	0.88	NA	
Pathologic factors					
T stage					
T1	333 (68.0%)	157 (32.0%)	1	Ref	
T2	364 (60.1%)	242 (39.9%)	1.44	1.12–1.85	.005*
T3	873 (65.1%)	468 (34.9%)	1.19	0.95–1.49	.139
T4	641 (70.4%)	270 (29.6%)	1.05	0.82–1.33	.716
Unknown	1,105 (76.4%)	342 (23.6%)	0.84	0.65–1.07	.157
N stage					
N0	1,211 (65.2%)	646 (34.8%)	1	Ref	
N1	878 (68.6%)	401 (31.4%)	0.90	0.77–1.06	.202
N2	251 (63.1%)	147 (36.9%)	1.21	0.95–1.54	.115
N3	89 (69.0%)	40 (31.0%)	0.98	0.66–1.46	.928
Unknown	887 (78.4%)	245 (21.6%)	0.60	0.48–0.75	<.001*
AJCC stage group					
I	513 (64.3%)	285 (35.7%)			
II	750 (66.5%)	378 (33.5%)			
III	934 (67.2%)	455 (32.8%)			
Unknown	1,119 (75.6%)	361 (24.4%)			

Abbreviations: CRT, chemoradiation; NA, not applicable; OR, odds ratio.
*Statistically significant

in 1,389 patients with stage III cancer (HR, 0.90; 95% CI, 0.79–1.02; $P=.106$).

Conditional landmark analyses at time points of 3 and 6 months were performed, excluding patients who were lost to follow-up or who died before

the specified landmark. In the 3-month conditional landmark analysis, CRT was associated with improved OS in a sample of 3,885 patients (HR, 0.86; 95% CI, 0.80–0.93; $P<.001$). In the 6-month conditional landmark analysis, CRT was associated with

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Figure 2. Survival analysis of patients treated with chemotherapy (chemo) alone or chemoradiation (CRT). (A) Kaplan-Meier curves of survival without adjustment. (B) Kaplan-Meier curves of survival with adjustment using propensity score matching for CRT use.

improved OS in a sample of 3,140 patients (HR, 0.83; 95% CI, 0.76–0.91; $P < .001$).

PSM Analysis

PSM was performed, adjusting for CRT use. A total of 2,678 patients with complete follow-up data were included in the final matched cohort: 1,339 receiving CRT and 1,339 receiving chemotherapy alone. Fig-

ure 2B illustrates Kaplan-Meier survival curves, and Table 4 shows the results of Cox proportional hazards regression in the matched cohort. After adjustment for CRT use with PSM, CRT was persistently associated with improved OS compared with chemotherapy alone (HR, 0.80; 95% CI, 0.74–0.88; $P < .001$).

Discussion

To our knowledge, this is the first published study in the contemporary era comparing CRT with chemotherapy alone for nonmetastatic gastric cancer.

Table 3. Multivariable Cox Proportional Hazard Models for OS Without Propensity Score Adjustment

Significant Factors	Hazard of Death (95% CI)	P Value
Year of diagnosis		
2004–2006	Ref	
2007–2009	0.88 (0.80–0.96)	.005*
2010–2012	0.80 (0.73–0.88)	<.001*
2013–2015	0.74 (0.67–0.83)	<.001*
Age, y		
<65	Ref	
≥65	1.08 (1.01–1.17)	.030*
Charlson-Deyo comorbidity score		
0	Ref	
1	1.08 (0.99–1.18)	.074
≥2	1.21 (1.07–1.36)	.002*
Facility region		
Northeast	Ref	
South	1.13 (1.03–1.23)	.009*
Midwest	1.28 (1.16–1.42)	<.001*
West	1.20 (1.07–1.34)	.002*
Unknown	NA	
Race		
Non-Hispanic white	Ref	
Black	0.84 (0.77–0.92)	<.001*
Other	0.69 (0.63–0.75)	<.001*
Unknown	0.82 (0.55–1.23)	.344
Facility type		
Academic/Research	Ref	
Community/Comprehensive community	1.11 (1.04–1.19)	.003
Unknown	NA	
T stage		
T1	Ref	
T2	0.97 (0.84–1.12)	.658
T3	0.99 (0.87–1.13)	.906
T4	1.29 (1.13–1.47)	<.001*
Unknown	1.08 (0.95–1.24)	.246
N stage		
N0	Ref	
N1	1.02 (0.94–1.12)	.591
N2	1.14 (1.00–1.31)	.059
N3	1.12 (0.89–1.41)	.352
Unknown	1.25 (1.13–1.39)	<.001*
Treatment received		
Chemotherapy alone	Ref	
CRT	0.82 (0.77–0.89)	<.001*

Abbreviations: CRT, chemoradiation; NA, not applicable; OS, overall survival.
*Statistically significant.

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Table 4. Multivariable Cox Proportional Hazard Models for OS Adjusted With Propensity Score for CRT Use

Significant Factors	Hazard Ratio (95% CI)	P Value
Year of diagnosis		
2004–2006	Ref	
2007–2009	0.90 (0.80–1.01)	.082
2010–2012	0.81 (0.72–0.92)	.001*
2013–2015	0.75 (0.66–0.86)	<.001*
Age, y		
<65	Ref	
≥65	1.08 (0.98–1.19)	.134
Charlson-Deyo comorbidity score		
0	Ref	
1	1.06 (0.95–1.18)	.280
≥2	1.21 (1.05–1.38)	.007*
Facility region		
Northeast	Ref	
South	1.10 (0.98–1.23)	.112
Midwest	1.24 (1.10–1.41)	.001*
West	1.20 (1.04–1.38)	.015*
Unknown	NA	
Race		
Non-Hispanic white	Ref	
Black	0.87 (0.78–0.97)	.015*
Other	0.66 (0.58–0.74)	<.001*
Unknown	1.19 (0.69–2.07)	.527
Facility type		
Academic/Research	Ref	
Community/Comprehensive community	1.09 (1.00–1.19)	.061
Unknown	NA	
T stage		
T1	Ref	
T2	1.01 (0.86–1.18)	.945
T3	0.95 (0.82–1.11)	.540
T4	1.35 (1.16–1.58)	<.001*
Unknown	1.10 (0.94–1.29)	.231
N stage		
N0	Ref	.511
N1	1.04 (0.93–1.15)	.308
N2	1.09 (0.92–1.30)	.239
N3	1.19 (0.89–1.60)	<.001*
Unknown	1.28 (1.11–1.47)	.511
Treatment received		
Chemotherapy alone	Ref	
CRT	0.80 (0.74–0.88)	<.001*

Abbreviations: CRT, chemoradiation; NA, not applicable; OS, overall survival.
*Statistically significant.

We found that, in the absence of surgical resection, receipt of CRT was associated with significantly improved survival compared with chemotherapy alone. On subset analysis, a survival benefit was seen for patients with overall stage I and II gastric cancer and a trend toward benefit in those with stage III cancer.

Three previous trials have investigated nonsurgical management of locally advanced gastric cancer, although all used outdated chemotherapy and RT techniques. A randomized trial from the Mayo Clinic published in 1969 found a benefit for combined CRT, with a 5-year OS rate of 12% versus 0% in those receiving chemotherapy alone.¹⁹ A GITSG trial published in 1982 demonstrated improved

survival at 4 years when adding RT to 5-FU and methyl-CCNU¹⁸; a subsequent GITSG trial that added doxorubicin found no benefit for RT.¹⁷ In the modern era, no trials have compared chemotherapy and CRT in the definitive setting. In the adjuvant setting, prior studies suggest a benefit for RT in cases of inadequate surgery. The Intergroup 0116 trial found that adjuvant CRT was associated with an improvement in 3-year OS compared with observation.⁶ This survival benefit is frequently attributed to inadequate nodal dissection due to 54% of patients undergoing D0 nodal dissection. Additionally, post hoc analysis of the Dutch Gastric Cancer Group randomized trial of D1 versus D2 nodal dissection found benefit for adjuvant CRT in patients with D1 nodal dissection or positive surgical margins.²⁶ Other retrospective analyses have also consistently found OS benefit for CRT in patients with positive surgical margins or inadequate nodal dissection.^{27–29}

Our findings are consistent with the current NCCN Guidelines delineating CRT as a treatment option for unresectable stage I–III gastric cancer, with our analysis showing improved survival associated with CRT compared with chemotherapy alone.¹⁴ Furthermore, these findings suggest that CRT should be incorporated into other guidelines, such as those from ESMO and JGCA, which currently do not mention CRT as a potential treatment regimen.^{15,16} We note that the NCDB captures only US patients. The overall rate of CRT use in our cohort was 30.8%, but other countries may have significantly lower rates due to the omission of this treatment option from their guidelines.

In our study, patients receiving CRT had a 2-year OS rate of 28.3% and median survival of 12.3 months versus 21.5% and 11.3 months, respectively, for the chemotherapy-alone group. We speculate that our study may actually underestimate the true survival benefit of CRT. First, we included patients receiving palliative and definitive doses of RT to avoid biasing our comparison. In some patients, RT may have been delivered with the intention of palliating bleeding or obstructive symptoms, rather than for definitive treatment. Additionally, we observed indications of adverse selection bias in the CRT group, as CRT use was associated with several adverse risk factors, including higher comorbidity score and older age. Finally, the HR was more favorable for CRT after propensity score adjustment (0.82 vs 0.80). Indeed, 2 recent phase II

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trials investigating CRT regimens demonstrated considerably superior survival outcomes: Wydmanski et al²⁰ and Liu et al²¹ reported median survivals of 17.1 and 25.8 months, respectively, and 3-year OS rates of 48% and 52%, respectively.

These results have additional implications for the design of clinical trials. We conducted a search using the terms “unresectable,” “inoperable,” and “gastric cancer” on ClinicalTrials.gov and identified at least 10 currently ongoing phase I/II trials investigating chemotherapy-alone regimens as first-line therapy, with eligibility criteria grouping metastatic gastric cancer with locally advanced, unresectable gastric cancer (ClinicalTrials.gov identifiers: NCT00515411, NCT02076594, NCT00183898, NCT03283761, NCT00952003, NCT01913639, NCT03281369, NCT02746796, NCT02504229, NCT01295086). Numerous completed trials on ClinicalTrials.gov and several recently published studies have similar eligibility criteria.^{30–32} We hypothesize that the lower CRT use in academic versus community centers observed in our analysis is partly due to enrollment into such trials. Clinicians should have a comprehensive, individualized discussion of treatment options, including CRT for patients undergoing therapy for nonmetastatic disease.

Our study is subject to the usual biases of retrospective database studies, including limitations in the ability to control for confounding variables and variation in survival data collection methods.³³ We also note several limitations of the NCDB that are relevant to the current analysis. First, the NCDB

does not contain any information regarding treatment intent. Both chemotherapy and CRT regimens aimed at conversion to resectability have shown promising results.^{34–38} However, patients who convert to resectability and proceed to surgery as a result of initial treatment were excluded from our comparison. Additionally, patients treated with neoadjuvant chemotherapy with initial intent for surgery who did not proceed to resection or those treated with initial intent for sequential CRT who did not receive RT, were included in the chemotherapy-alone group. Second, all patients in this sample were clinically staged, and therefore evaluation of T and N stage was limited, with many patients marked as unknown. Third, guarantee-time bias could potentially have skewed our results, although we sought to mitigate this effect through a conditional landmark analysis. Despite these limitations, the large sample of patients in this study provides considerable value in the absence of randomized data.

Conclusions

We found that CRT was associated with improved survival compared with chemotherapy alone in patients with unresected stage I–III gastric cancer. Only 30.8% of patients in this population received CRT. This survival benefit for CRT is discordant with European and Japanese treatment guidelines, as well as eligibility criteria for numerous ongoing clinical trials. Further prospective studies are needed to evaluate the role of RT for these patients.

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