Original Article

Adjuvant Radiotherapy Improves Overall Survival in Patients With Resected Gastric Adenocarcinoma: A National Cancer Data Base Analysis

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BACKGROUND: For patients with resectable gastric adenocarcinoma, perioperative chemotherapy and adjuvant chemoradiotherapy (CRT) are considered standard options. In the current study, the authors used the National Cancer Data Base to compare overall survival (OS) between these regimens. **METHODS:** Patients who underwent gastrectomy for nonmetastatic gastric adenocarcinoma from 2004 through 2012 were divided into those treated with perioperative chemotherapy without RT versus those treated with adjuvant CRT. Survival was estimated and compared using univariate and multivariate models adjusted for patient and tumor characteristics, surgical margin status, and the number of lymph nodes examined. Subset analyses were performed for factors chosen a priori, and potential interactions between treatment and covariates were assessed. **RESULTS:** A total of 3656 eligible patients were identified, 52% of whom underwent perioperative chemotherapy and 48% of whom received postoperative CRT. The median follow-up was 47 months, and the median age of the patients was 62 years. Analysis of the entire cohort demonstrated improved OS with adjuvant RT on both univariate (median of 51 months vs 42 months; $P = .013$) and multivariate (hazard ratio, 0.874; 95% confidence interval, 0.790-0.967 [$P = .009$]) analyses. Propensity score-matched analysis also demonstrated improved OS with adjuvant RT (median of 49 months vs 39 months; $P = .033$). On subset analysis, a significant interaction was observed between the survival impact of adjuvant RT and surgical margins, with a greater benefit of RT noted among patients with surgical margin-positive disease (hazard ratio with RT: 0.650 vs 0.952; P for interaction $<.001$). **CONCLUSIONS:** In this National Cancer Data Base analysis, the use of adjuvant RT in addition to chemotherapy was associated with a significant OS advantage for patients with resected gastric cancer. The survival advantage observed with adjuvant CRT was most pronounced among patients with positive surgical margins. ***Cancer*** **2017;123:3402-9**. © *2017 American Cancer Society.*

KEYWORDS: adenocarcinoma, chemoradiotherapy (CRT), conformal radiotherapy, gastrectomy, stomach.

INTRODUCTION

According to the National Cancer Institute's Surveillance, Epidemiology, and End Results program, approximately 26,370 new cases of gastric cancer are expected to have been diagnosed in 2016, and the estimated number of deaths is 10,730, with a low survival rate of 30.4% at 5 years.[1] Gastric cancer is an even more prevalent malignancy worldwide, representing the fifth most common cancer and the third leading cause of cancer mortality.[2]

The primary treatment for patients with early-stage disease is surgical resection, with a goal for an R0 resection with surgical margins measuring ≥4 cm. The consensus National Comprehensive Cancer Network (NCCN) guidelines recommend gastrectomy with D1 or modified D2 lymph node dissection (LND) with a goal of removing ≥15 lymph nodes for those cases of resectable gastric cancer.[3]

The role of radiotherapy (RT) in patients with gastric cancer has been controversial. The Southwest Oncology Group (SWOG) 9008/INT-0116 study demonstrated improved overall survival (OS) and recurrence-free survival in those patients who received postoperative chemoradiotherapy (CRT) compared with those who underwent observation after surgery.[3] The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial evaluated perioperative chemotherapy versus surgery alone for patients with resectable gastroesophageal cancer, and reported that chemotherapy with epirubicin, cisplatin, and infused 5-fluorouracil improved OS and progression-free survival.[4] To the best of our knowledge, only 1 trial to date has presented evidence comparing perioperative chemotherapy with adjuvant CRT in patients with gastric cancer. However, this multicenter randomized phase III trial of neo-adjuvant chemotherapy

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followed by surgery and chemotherapy or by surgery and CRT in resectable gastric cancer (CRITICS) trial has not yet been published in peer-reviewed article form though has been presented in abstract form.[5] Currently, both perioperative chemotherapy and adjuvant CRT strategies remain prevalent in clinical practice. In this analysis, we evaluated outcomes with perioperative chemotherapy and adjuvant CRT using the National Cancer Data Base (NCDB).

MATERIALS AND METHODS

Data Source and Patient Selection

The NCDB is jointly sponsored by the American College of Surgeons and the American Cancer Society. It is a clinical oncology database compiled from hospital registry data collected by >1500 Commission on Cancer-accredited facilities tracking treatment and outcomes of patients. This database represents >70% of newly diagnosed malignancies throughout the United States and Puerto Rico.[6] 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.

A total of 39,908 adult patients (aged ≥18 years) were identified who were diagnosed with gastric cancer between 2004 and 2012. This data set then was limited to patients with adenocarcinoma histology (using *International Classification of Diseases for Oncology, 3rd Edition* [ICD-O-3] codes), known clinical T classification (cT) and clinical N classification (cN), clinical nonmetastatic (cM) disease, known status after gastrectomy, and known receipt of chemotherapy and RT (with a defined dose range of 4500-5040 cGy as recommended by NCCN guidelines for those receiving RT).[7] Patients with unknown vital status were excluded. This resulted in a total of 3656 evaluable patients (Fig. 1).

Patient Demographics and Treatment Variables

Pertinent patient demographics and treatment characteristics were included in this analysis. Race was categorized as white, African American, other, and unknown. Patient comorbidities were assessed using the Charlson-Deyo comorbidity (CDC) score (0, 1, or ≥2). The American Joint Committee on Cancer (AJCC) staging system was used to determine the cT, cN, and cM classifications.[8] Because both the sixth and seventh editions of the AJCC staging system were applicable during the designated time frame, those coded using the sixth edition were converted to seventh edition staging guidelines. RT was limited to the dose ranges previously specified and was coded as external beam RT. RT was designated as postoperative by coding of sequence with receipt of RT after gastrectomy in the NCDB. Chemotherapy was specified as preoperative or postoperative using the number of days from diagnosis to the initiation of chemotherapy and the start of surgery. Surgery was coded as gastrectomy in the NCDB; patients undergoing biopsy only or local excision were excluded. Surgical margin status is documented in the NCDB and was recorded as positive, negative, or not evaluated. The number of lymph nodes examined also is documented in the NCDB and was classified further as 0, 1 to 14, 15 to 25, or ≥26 lymph nodes to serve as general surrogates of D0, D1, or D2 resections, derived from the average number of lymph nodes investigated in the Dutch trial (18.4 lymph nodes in the D1 group vs 31.5 lymph nodes in the D2 group)[9] and the UK Medical Research Council Trial[10] (median number of lymph nodes: 13 in D1 resection vs 17 in D2 resection).

Statistical Analysis

All statistical analyses were performed using SPSS statistical software (version 23.0; IBM Corporation, Armonk, NY). The median follow-up was calculated using the reverse Kaplan-Meier method.[11] Pearson chi-square tests were used to assess associations between categorical variables and treatment group. The OS interval was calculated from the date of diagnosis to the date of death. OS was estimated using the Kaplan-Meier method. Univariate survival analysis was performed with the log-rank test, with Cox proportional hazards regression used to estimate hazard ratios (HRs). Multivariate analysis (MVA) was performed adjusted for cofactors of age, sex, race, cT classification (1-4), cN classification (0-3), surgical margin status (positive vs negative), number of lymph nodes examined, and CDC scores (0 to ≥2). Patient, clinical, and treatment variables were selected a priori. The proportional hazards assumption was assessed for all variables used in MVA and returned no significant results.[12] Subset analyses also were performed for factors selected a priori, including surgical margin status, the number of lymph nodes examined, cT classification, and cN classification. Potential interactions between treatment and covariates were assessed using MVA Cox models adjusted for all aforementioned cofactors.

Propensity score-matched analyses were performed comparing outcomes for perioperative chemotherapy versus adjuvant CRT. One-to-one matching without replacement was completed using the nearest-neighbor match on

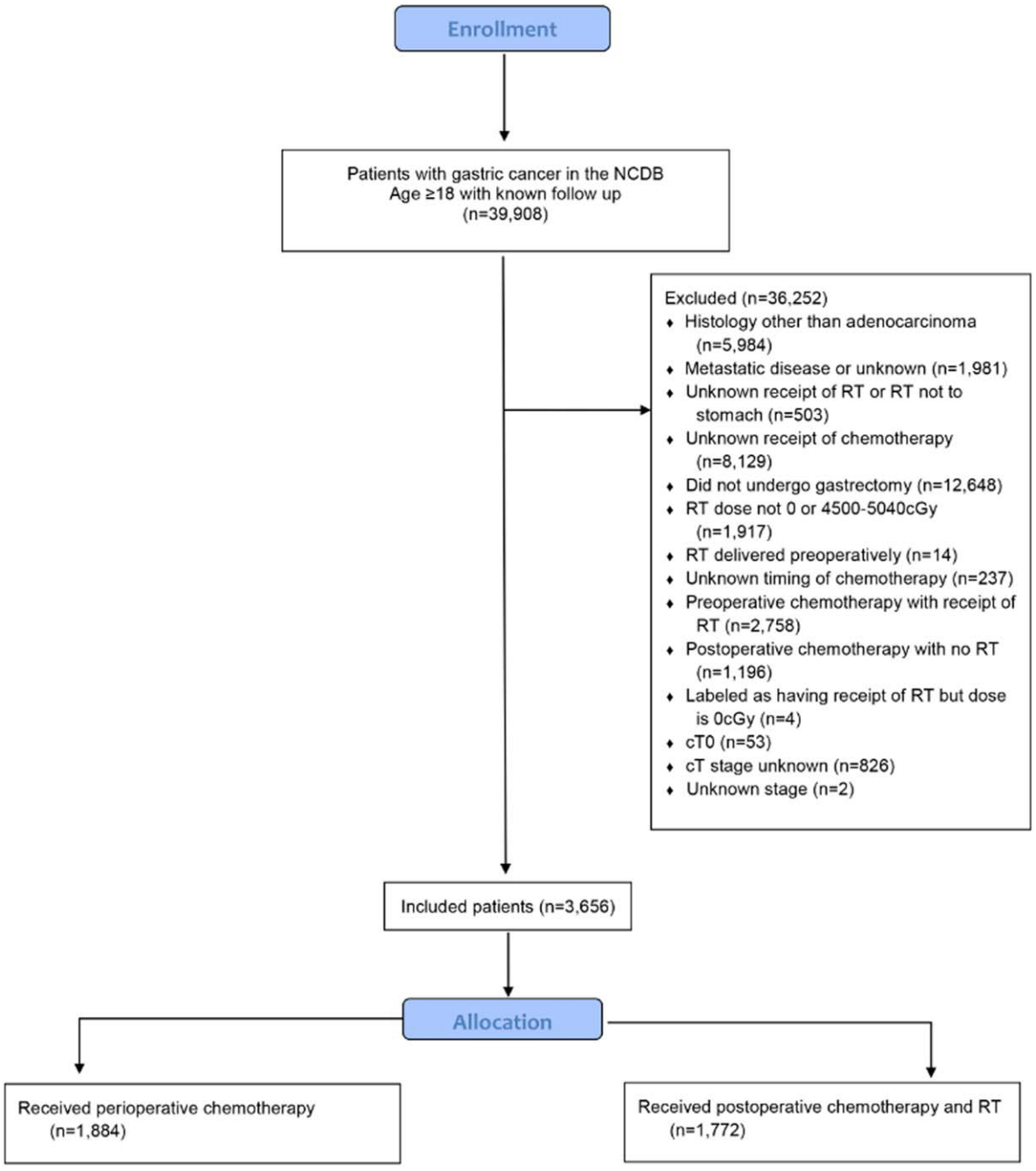

Figure 1. Cohort derivation showing case selection for the study group. cGy indicates centigrays; cT, clinical tumor classification; NCDB, National Cancer Data Base; RT, radiotherapy.

the logit of the propensity score for the RT approach (derived from the variables of age, sex, race, CDC score, cT classification, cN classification, number of lymph nodes examined, and surgical margin status). The caliper width was 0.05 times the standard deviation of the logit of the propensity score, which is estimated to eliminate >99% of the bias due to cofounding variables.[13,14]

RESULTS

Patient Characteristics

A total of 3656 patients were included in the current study, 1884 of whom (52%) underwent perioperative chemotherapy and 1772 of whom (48%) received postoperative chemotherapy and RT. By stage of disease, 29.0% of patients were classified as stage I, 53.1% as stage II, and

TABLE 1. Patient and Disease Characteristics

Variables	All Patients		Radiotherapy		No Radiotherapy		*P*
	No.	%	No.	%	No.	%	
Age, y							.14
<65	2127	58.2	1029	58.1	1098	58.3	
≥65	1529	41.8	743	41.9	786	41.7	
Race							<.01
White	2632	72.0	1190	67.2	1442	76.5	
African American	588	16.1	327	18.5	261	13.9	
Other/unknown	436	11.9	255	14.3	181	9.6	
Sex							<.01
Male	2381	65.1	1113	62.8	1268	67.3	
Female	1275	34.9	659	37.2	616	32.7	
Charlson-Deyo comorbidity score							.63
0	2713	74.2	1321	74.5	1392	73.9	
1	751	20.5	354	20.0	397	21.1	
≥2	192	5.3	97	5.5	95	5.0	
Clinical T classification							<.01
1	542	14.8	340	19.2	202	10.7	
2	1028	28.1	587	33.1	441	23.4	
3	1717	47.0	648	36.6	1069	56.7	
4	369	10.1	197	11.1	172	9.1	
Clinical N classification							<.01
0	1709	46.7	905	51.1	804	42.7	
1	1365	37.3	522	29.5	843	44.7	
2	411	11.2	220	12.4	191	10.1	
3	171	4.7	125	7.1	46	2.4	
AJCC 7th edition clinical stage of disease							<.01
I	1061	29.0	647	36.5	414	22.0	
II	1942	53.1	769	43.4	1173	62.2	
III	653	17.9	356	20.1	297	15.8	
Surgical margin status							<.01
Positive	528	14.4	285	16.1	243	12.9	
Negative	3023	82.7	1444	81.5	1579	83.8	
Not evaluated/unknown	105	2.9	43	2.4	62	3.3	
No. of lymph nodes examined							<.01
0	128	3.5	43	2.4	85	4.5	
1-14	1299	35.5	729	41.1	570	30.3	
15-25	1331	36.4	631	35.6	700	37.2	
≥26	851	23.3	356	20.1	495	26.3	
Unknown	47	1.3	13	0.7	34	1.8	

Abbreviation: AJCC, American Joint Committee on Cancer.

17.9% as stage III. The median follow-up was 47 months (range, 1-128 months). The median age of the patients was 62 years (range, 19-90 years), and the majority were male (65.1%) and white (72%). The majority of the patients (74.2%) presented with a modified CDC score of 0. Table 1 shows patient and disease characteristics.

Overall Survival

Analyses of the entire cohort demonstrated improved OS with adjuvant RT on both univariate survival analysis (median OS: 51 months vs 42 months [log-rank $P = .013$]; 5-year OS rate: 46% [95% confidence interval (95% CI), 43%-49%] vs 41% [95% CI, 38%-44%]) and MVA (HR, 0.874; 95% CI, 0.790-0.967 [$P = .009$]). Kaplan-Meier survival curves are shown in Figure 2 Top. A propensity score-matched analysis was performed that confirmed well-balanced baseline patient characteristics (Table 2). In this matched analysis, adjuvant RT continued to be associated with improved OS (5-year OS rate: 45% [95% CI, 42%-49%] vs 42% [95% CI, 38%-45%]; median, 49 months vs 39 months [HR, 0.886; 95% CI, 0.793-0.990] [$P = .033$]) (Fig. 2 Bottom).

Subgroup Analyses

A significant interaction was observed between the survival impact of adjuvant RT and surgical margins, with a greater benefit of RT noted among patients with surgical margin-positive disease (*P* for interaction <.001). Adjusting for the variables of age, sex, race, CDC score, cT classification, cN classification, number of lymph nodes examined, and surgical margin status, patients with positive surgical margins achieved superior OS with RT

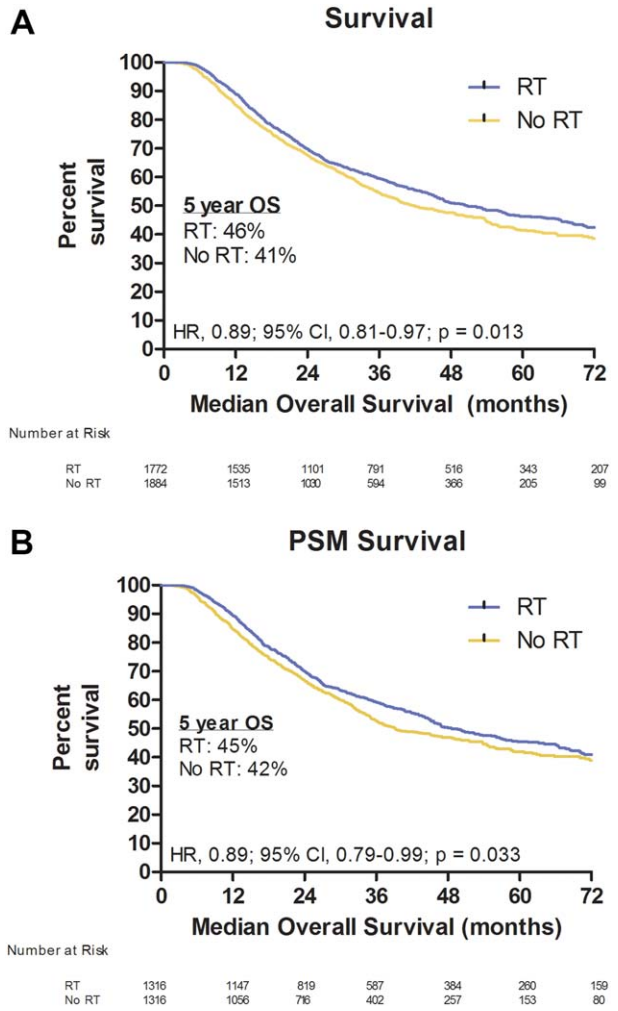

Figure 2. Overall survival (OS) for patients with resected gastric cancer comparing perioperative chemotherapy alone with postoperative chemotherapy and radiotherapy (RT) in (*Top*) all patients and (*Bottom*) propensity score-matched (PSM) patients.

(median, 27 months vs 20 months; multivariate HR, 0.650 [$P<.001$]), whereas the differences in OS did not reach statistical significance for patients with surgical margin-negative disease (median, 59 months vs 54 months; multivariate HR, 0.952 [$P = .408$]). No significant differences in the impact of adjuvant RT were observed by cT classification, cN classification, or extent of LND (Fig. 3).

DISCUSSION

The role of RT in the treatment of patients with gastric cancer remains controversial. In the setting of resectable gastric cancer, 2 randomized trials have compared surgery alone versus surgery followed by RT or chemotherapy. The British Stomach Cancer Group randomized patients to surgery alone or surgery and RT. No survival benefit was found, although a significant decrease in locoregional disease recurrence was found in those patients receiving RT.[15] Zhang et al randomized patients to preoperative RT versus surgery alone, and reported a significant improvement in survival with RT and improved surgical resection rates.[16] A more recent meta-analysis evaluating the role of preoperative, postoperative, and intraoperative RT in patients with resectable gastric cancer demonstrated a significant improvement in OS at 5 years among patients who underwent RT (defined as preoperative, postoperative, or intraoperative) in addition to surgery.[17]

The roles of combined modality therapy also have been explored and define the current standard of care for patients with locally advanced gastric cancer. The well-known SWOG 9008/INT-0116 trial evaluated the role of postoperative CRT in individuals with resectable gastric or gastroesophageal junction cancer.[18] Patients with $\geq$T3 and/or lymph node-positive disease were randomized to surgery alone (R0 surgical resection) versus surgery plus postoperative CRT. Postoperative CRT demonstrated a significant improvement in OS (median OS in patients treated with surgery alone vs postoperative CRT: 27 months vs 36 months, respectively) and recurrence-free survival. No significant increase in late toxicities was noted. These results remained significant in an updated analysis with a median follow-up of 10 years.[3] Notably, the majority of patients underwent an incomplete LND, with only 10% of patients undergoing a D2 LND. The phase 3 "MAGIC" trial compared perioperative chemotherapy with the combination of epirubicin, cisplatin, and infused 5-fluorouracil (3 cycles preoperatively and 3 cycles postoperatively) versus surgery alone for patients with resectable gastric cancer.[4] RT was not administered either before or after surgery. The patients who received perioperative chemotherapy were found to have a higher likelihood of progression-free survival and OS, with a 5-year survival rate of 36% versus 23%.

In the recent Adjuvant Chemoradiotherapy in Stomach Tumors (ARTIST) trial, postoperative CRT with capecitabine and cisplatin did not appear to significantly decrease disease recurrence after a D2 LND compared with adjuvant chemotherapy alone. A subgroup analysis of patients with lymph node-positive disease found a significant increase in 3-year disease-free survival (DFS) in the postoperative CRT group compared with postoperative chemotherapy alone.[19] Of note, patients with positive surgical resection margins after surgery were excluded from the ARTIST trial. In the ongoing ARTIST

TABLE 2. Propensity Score-Matched Analysis

Variables	Radiotherapy		No Radiotherapy		*P*
	No.	%	No.	%	
All	1316	100	1316	100	
Age, y					.33
>62	650	49	625	47	
≤62	666	51	691	53	
Race					.89
White	948	72	956	73	
African American	222	17	208	16	
Other/unknown	146	11	152	12	
Sex					.63
Male	833	63	845	64	
Female	483	37	471	36	
Charlson-Deyo comorbidity score					.58
0	973	74	990	75	
1	279	21	258	20	
≥2	64	5	68	5	
No. of lymph nodes examined					.89
0	42	3	41	3	
1-14	468	36	480	36	
15-25	499	38	501	38	
≥26	295	22	286	22	
Unknown	12	1	8	1	
Clinical T classification					.72
1	199	15	192	15	
2	397	30	403	31	
3	595	45	580	44	
4	125	9	141	11	
Clinical N classification					.83
0	643	49	645	49	
1	462	35	466	35	
2	157	12	160	12	
3	54	4	45	3	
Surgical margin status					.85
Positive	199	15	191	15	
Negative	1090	83	1095	83	
Not evaluated/unknown	27	2	30	2	

2 trial, patients with positive lymph nodes after D2 LND are randomized to receive postoperative chemotherapy or CRT. In the current NCDB analysis, differences in the impact of adjuvant RT by lymph node stage and extent of LND did not reach statistical significance, although potential differences in DFS could not be evaluated.

The CRITICS study, a multicenter, randomized phase 3 trial, compared perioperative chemotherapy with preoperative chemotherapy and postoperative CRT in patients who underwent adequate (D2) LND.[5] Although presented in abstract form only, the results demonstrated no benefit for postoperative CRT. The 5-year OS rate was 41.3% for patients in the chemotherapy alone arm versus 40.9% for those treated with CRT ($P = .99$). It is interesting to note that only 46% and 55% of patients, respectively, completed postoperative chemotherapy and CRT.

In this NCDB analysis, a 5% absolute OS advantage was observed at 5 years with the use of adjuvant RT in addition to chemotherapy for patients with resected gastric cancer (5-year OS rate: 46% [95% CI, 43%-49%] vs 41% [95% CI, 38%-44%]), which remained significant on MVA and propensity score-matched analyses. The finding of an OS advantage with RT when controlling for confounding using both multivariate adjustment in the overall cohort as well as propensity score matching with well-matched baseline characteristics supports the observation of an association between treatment strategy and survival in this registry data set. The relative survival advantage observed with adjuvant RT was particularly evident among patients with positive surgical margins, whereas the impact of RT was not significantly modified by the cT classification, cN classification, or extent of LND. The contemporary NCCN guidelines advocate postoperative RT for patients who undergo either R1 or R2 gastric resections and the results of the current study support that recommendation, with the observation of a 7-month median OS advantage with RT for patients with positive surgical

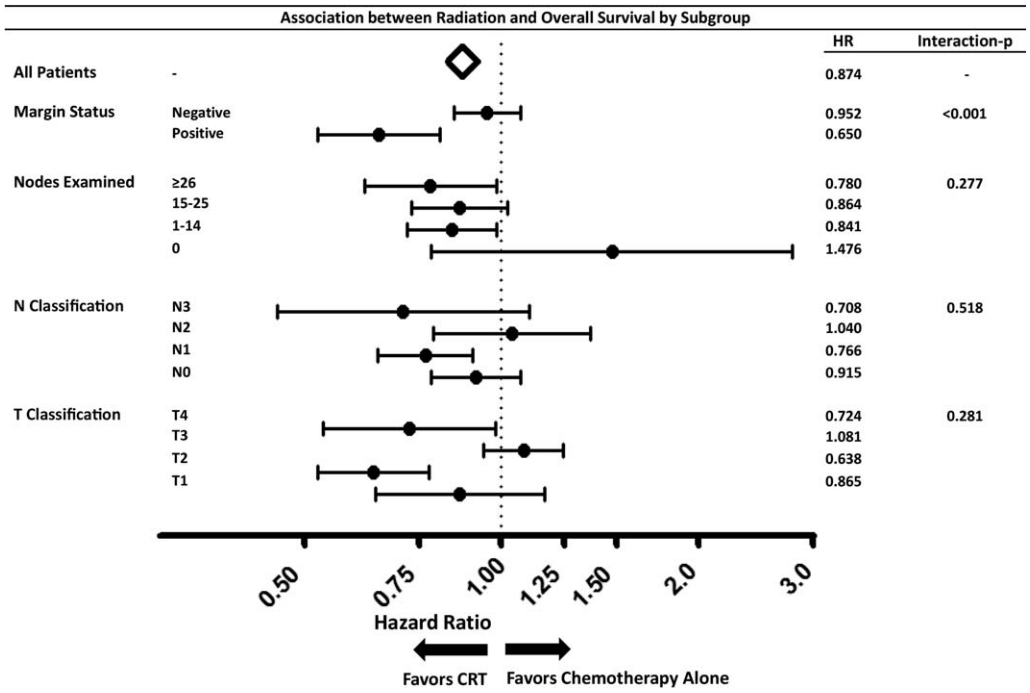

Figure 3. Forest plot of the association between radiotherapy and overall survival by patient subgroup. CRT indicates chemoradiotherapy; HR, hazard ratio; N, lymph node classification; T, tumor classification.

margins (median OS, 27 months vs 20 months; HR, 0.650 [$P<.001$]).

The current study has several limitations. Given the retrospective design, all analyses are subject to the critical limitation of selection bias. Although MVA, propensity score-matching analysis, and subgroup analysis were undertaken to account for this limitation, these techniques cannot account for potentially significant imbalances in unknown confounders. Data regarding specific chemotherapy regimens were not available for analyses. In addition, all analyses were limited to OS, with no data available concerning more granular endpoints including locoregional control, DFS, salvage therapy, and quality of life. An assumption of this analysis is that the majority of patients receiving preoperative chemotherapy would have been recommended to follow a regimen including planned postoperative chemotherapy (to comprise the perioperative chemotherapy group). It is important to acknowledge as a limitation that a percentage of patients in this group likely did not receive postoperative chemotherapy. However, this may represent a real-world consideration for perioperative chemotherapy regimens, because even in the MAGIC trial only 66% of patients who completed preoperative chemotherapy went on to initiate postoperative chemotherapy and, of those, only 76% completed the 3 recommended cycles.[4] Similarly, patients who received RT were included with doses of 45 to 50.4 Gy, which may exclude some patients who were unable to complete RT secondary to toxicity, therefore making the RT cohort appear more favorable. Finally, inherent to all large database analyses is the concern of missing data. The current study was limited to patients with known receipt of RT, chemotherapy, gastrectomy, histology, and vital status, which resulted in the exclusion of a large number of patients to generate a data set that was complete for covariates relevant to treatment selection and survival.

The major strengths of the current study are that it represents real-world evidence and the findings complement the conclusions of randomized trials examining this issue.[20] Furthermore, it demonstrates a survival impact for RT that is generalizable across a large population.

Conclusions

The role of RT in the management of patients with resected gastric cancer is controversial. In this NCDB analysis, we observed improved OS with RT in a large cohort of patients in the United States with resected gastric cancer. Current NCCN guidelines recommend the consideration of RT for patients undergoing R1 and R2 surgical resections, and the current NCDB analysis

strongly supports that recommendation, particularly in the setting of positive surgical margins. Forthcoming analyses from completed and ongoing randomized trials will continue to elucidate the role and optimal patient selection for adjuvant RT for this challenging disease.

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CONFLICT OF INTEREST DISCLOSURES

Bernard L. Jones receives research funding from Varian Medical Systems for work performed outside of the current study. He also has a patent pending for a technique to identify fiducial markers in x-ray images.

AUTHOR CONTRIBUTIONS

Priscilla K. Stumpf, **Tracey E. Schefter**, **Karyn A. Goodman**, and **Chad G. Rusthoven** were responsible for conceptualization, methodology, analysis, and writing. **Arya Amini**, **Bernard L. Jones**, **Matthew Koshy**, **David J. Sher**, and **Christopher H. Lieu** were responsible for methodology, analysis, and writing. **Chad G. Rusthoven** was responsible for supervision. **Priscilla K. Stumpf**, **Arya Amini**, **Bernard L. Jones**, **Matthew Koshy**, **David J. Sher**, **Christopher H. Lieu**, **Tracey E. Schefter**, **Karyn A. Goodman**, and **Chad G. Rusthoven** have read and approved the article. This article is not under consideration elsewhere.

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