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Comparison of Perioperative and Histopathologic Outcomes among Neoadjuvant Treatment Strategies for Locoregional Gastric Cancer

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Abstract

BACKGROUND and OBJECTIVES—Neoadjuvant chemotherapy (NAC) and chemoradiation (NCRT) have demonstrated improved survival for gastric cancer. However, the optimal neoadjuvant treatment remains unclear. We sought to evaluate perioperative and histopathologic outcomes among neoadjuvant treatments for locoregional gastric cancer.

METHODS—The National Cancer Database queried patients who received NAC or NCRT followed by resection for T2-T4 and/or node positive gastric cancer (2006-2018). Logistic and Poisson regression assessed perioperative (30-day readmission, 30- and 90-day mortality, length of stay (LOS)) and histopathologic outcomes (pathologic complete response (PCR), margin status, and negative pathologic lymph nodes (ypN0)). Kaplan-Meier methods and Cox regression assessed overall survival (OS).

RESULTS—Of 9,831 patients, 4,221 (42.9%) received NAC and 5,610 (57.1%) NCRT. There were no differences in perioperative outcomes, apart from patients treated with NCRT exhibiting increased LOS (IRR 1.09, 95%CI 1.03-1.16). Patients who received NCRT were more likely to achieve PCR, margin-negative resection, and ypN0 (all $p<0.05$). Median OS was 36.8 months for NAC and 33.6 months for NCRT ($p<0.001$). NCRT independently predicted worse OS (vs NAC, HR 1.10, 95%CI 1.03-1.18).

CONCLUSION—NCRT was associated with better histologic tumor response although NAC was associated with improved OS. Better understanding prognostication through histologic assessment following neoadjuvant therapy is needed.

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Keywords

locoregional gastric cancer; neoadjuvant treatment; chemotherapy; chemoradiation; perioperative outcomes; response to treatment

Introduction

Gastric cancer is the 5th most common cause of cancer related death worldwide, resulting in an estimated 11,090 deaths among 26,380 newly diagnosed gastric cancer cases in 2022.[1] Thus, identifying the optimal course of treatment to improve survival outcomes among patients with gastric cancer is of critical importance. Over the past two decades, the use of neoadjuvant treatments for patients with locoregional gastric cancer has expanded based on the published survival benefit in several randomized controlled trials.[2–4] The first of these landmark studies is the MAGIC trial, demonstrating that perioperative chemotherapy was associated with improved survival compared to surgery alone,[2] followed by the CROSS trial which established that neoadjuvant chemoradiation was associated with improved survival compared to surgery alone for patients with esophagogastric junctional tumors.[3] Most recently, the FLOT-4AIO trial demonstrated that perioperative fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) was associated with improved survival compared to the conventionally utilized epirubicin, cisplatin, and fluorouracil (ECF) regimen.[4]

Despite these trials, current National Comprehensive Cancer Network (NCCN) guidelines for patients with locoregional gastric cancer defined as those with T2-T4 and/or node positive disease recommend either upfront surgical resection, perioperative chemotherapy, or neoadjuvant chemoradiation as their first course of treatment.[5] Given these dissimilar treatment pathways, elucidation of these national guidelines is crucial to help standardize treatment selection and improve patient outcomes. To answer this empirical question, the TOPGEAR and CRITICS-II trials are currently underway to identify the optimal neoadjuvant treatment for patients with locoregional gastric cancer.[6,7] However, these randomized controlled trials are ongoing for which long-term results will likely not be published for several years.

Although preliminary results from previous trials have published equivalent safety profiles between neoadjuvant chemotherapy versus chemoradiation, differences in long-term survival have yet to be reported.[6–8] Additionally, as randomized controlled trials are typically limited to select, highly specialized centers, these results may not be truly reflective of short-term outcomes for patients with locoregional gastric cancer treated at cancer centers across the country. Thus, the objective of this study was to compare perioperative and histopathologic outcomes between patients who received neoadjuvant chemotherapy versus chemoradiation for patients with locoregional gastric cancer.

Materials and Methods

Data Source

This retrospective cohort study queried the National Cancer Database (NCDB) for patients diagnosed with gastric adenocarcinoma between January 1st 2006 and December 31st 2018.

[9] The NCDB is a nationwide registry that is jointly maintained by the American College of Surgeons' Commission on Cancer (CoC) and American Cancer Society, collecting data from patients treated at CoC-accredited hospitals as an obligatory component of accreditation. The NCDB is one of the largest and most detailed tumor registries in the country, identifying more than 70% of cancer cases across the US annually.[10,11] Details regarding data abstraction, sampling strategies, and variables collected within the NCDB have been previously described.[10,12,13] All data within the NCDB is completely deidentified and thus is Health Insurance Portability and Accountability Act compliant.

Patient Population

Patients aged 18 and older with a confirmed diagnosis of clinical T2-T4 and/or node positive gastric adenocarcinoma, using the International Classification of Disease for Oncology, third edition, were included.[14] We then identified patients who received neoadjuvant treatment, consisting of chemotherapy alone (NAC) versus chemoradiation (NCRT), followed by curative-intent resection. NAC was defined as patients who received systemic therapy before with or without further therapy after surgical resection while NCRT was defined as patients who received neoadjuvant chemotherapy with concomitant radiotherapy. Patients who presented with T1N0M0 or metastatic disease, underwent palliative-intent or upfront resection, or with any missing data were excluded (Supplemental Figure 1).

Primary and Secondary Outcomes

The primary outcomes of this study compared perioperative and histopathologic outcomes between patients who received NAC versus NCRT. Perioperative outcomes included 30-day readmission, 30-day mortality, 90-day mortality, and length of stay (LOS). Histopathologic outcomes included pathologic complete response (PCR), achieving an R0 resection with negative margins, and negative pathologic lymph nodes. Additionally, overall survival (OS) was compared between groups as a secondary outcome.

Statistical Analysis

Baseline patient demographics, hospital characteristics, and oncologic factors between patients who received NAC versus NCRT were compared using chi-square tests. Unadjusted analyses evaluating differences in perioperative and histopathologic outcomes were performed using chi-square tests and Wilcoxon rank-sum tests where appropriate. Significance was calculated for all statistical tests using a threshold of $\alpha < 0.05$. Multivariable logistic regression models using robust standard errors were constructed to assess the association of neoadjuvant treatment modalities with perioperative and histopathologic outcomes. A multivariable Poisson regression model was used to evaluate the association neoadjuvant treatment with LOS. Clinically relevant and statistically significant variables at the level of $\alpha < 0.05$ on unadjusted analyses were included in all multivariable models. Kaplan-Meier methods, in conjunction with log-rank tests, evaluated median OS. A multivariable cox proportional hazards regression was used to assess the association of neoadjuvant treatment with survival.

To account for potential selection bias regarding the use of NAC versus NCRT, a propensity-score-matching algorithm was employed. Propensity score matching was performed to match patients who received NAC with patients who received NCRT with a 1:1 ratio between groups based on age, race, Charlson-Deyo score, clinical T-category, clinical N-category, and year of diagnosis. Within the matched cohort unadjusted analyses were similarly utilized to compare perioperative and histopathologic outcomes using chi-squared and Wilcoxon rank-sum tests. Conditional logistic and Poisson regression models accounting for matching were constructed to evaluate the association between neoadjuvant treatments with perioperative and histopathologic outcomes. Kaplan-Meier methods as well as a conditional Cox proportional hazards regression model accounting for matching were performed to evaluate OS. All multivariable models were clustered at the facility level by a deidentified facility key. All analyses were performed using Stata MP Version 16.0 (Stata Corp, College Station, Texas).

Results

A total of 9,831 patients were identified with clinical T2-T4 and/or node positive gastric cancer who received neoadjuvant treatment followed by definitive surgical resection. Compared to patients who received NAC, patients who received NCRT were more commonly male (83.9% vs 66.2%, $p<0.001$) and non-Hispanic white (88.4% vs 58.1%, $p<0.001$) (Table 1). Additionally, patients who received NCRT most frequently had tumors located in the cardia of the stomach (94.6% vs 29.7%, $p<0.001$) while patients who received NAC more commonly had poorly differentiated tumors (65.0% vs 49.0%, $p<0.001$) with lymphovascular invasion (31.2% vs 16.5%, $p<0.001$), and node negative disease (42.8% vs 36.8%, $p<0.001$). A 1:1 propensity score match was then performed after which we identified a total of 5,894 patients with 2,947 in each cohort.

First, evaluated differences in the frequency of perioperative outcomes between groups. On unadjusted analysis, patients within the unmatched cohort who received NCRT had higher rates of 30-day readmission (6.9% vs 5.3%, $p=0.001$), 90-day mortality (5.7% vs 4.3%, $p=0.002$), and longer LOS (median 9 [IQR 7-13] vs median 8 [IQR 6-11], $p<0.001$) following their definitive surgical resection (Table 2). After 1:1 propensity score matching, patients who received NCRT still had increased rates of 30-day readmission (7.0% vs 5.7%, $p=0.042$) and LOS (median 9 [IQR 7-13] vs median 8 [IQR 6-11], $p<0.001$) when compared to patients who received NAC, although there was no longer a difference in 90-day mortality for perioperative outcomes.

To determine whether certain neoadjuvant treatments independently predicted specific perioperative outcomes, multivariable and Poisson regression models were performed for each individual outcome of interest while adjusting for potential confounders. For perioperative outcomes, patients who received NCRT had a 10% increased LOS (IRR 1.10, 95% CI 1.04-1.17) which remained significant after propensity score matching as well (Table 3). However, there was no difference in 30-day readmission or 30- or 90-day mortality between groups.

We then evaluated differences in histopathologic outcomes between patients who received NAC and NCRT with locoregional gastric cancer. On unadjusted analysis, patients within the unmatched cohort who received NCRT had higher rates of PCR (14.7% vs 7.2%, p<0.001), negative margins (95.6% vs 91.0%, p<0.001), and negative pathologic lymph nodes (59.2% vs 45.7%, p<0.001) when compared to patients who received NAC (Table 2). After performing a 1:1 propensity score match, the observation that patients who received NCRT more often achieved improved histopathologic outcomes remained significant for all three outcomes (all p<0.001).

To identify whether NCRT was independently predictive of improved histopathologic outcomes and not a result of potential confounders, multivariable regression models were similarly performed for each histopathologic outcome of interest. After adjusting for patient demographics, hospital factors, and tumor-specific characteristics, patients who received NCRT were more likely to achieve PCR (OR 1.58, 95%CI 1.28-1.93), negative margins (OR 1.62, 95%CI 1.24-2.12), and negative pathologic lymph nodes (OR 1.38, 95%CI 1.21-1.58) which similarly remained significant on adjusted multivariable models following propensity score matching (Table 3).

In order to understand if neoadjuvant treatment selection affects prognostication, we compared survival outcomes between patients who received NAC versus NCRT. For overall survival, patients who received NAC alone had improved OS (median 37.0 months [19.1-57.7] vs 33.8 months [17.4-56.4], p=0.018) (Figure 1a) compared to the NCRT group which remained significant within the propensity score matched cohort (median 36.8 months [18.7-58.4] vs 33.6 months [17.9-55.3], p=0.008) (Figure 1b). Similarly, after adjusting for potential confounders in a multivariable cox regression, patients who received NCRT were at increased risk of mortality compared to those who received NAC alone which remained significant after propensity score matching as well (HR 1.10, 95%CI 1.03-1.18) (Table 4).

Discussion

Over the past two decades, the use of NAC and NCRT have demonstrated improved survival for patients with gastric cancer compared to surgery alone.[2,3] However, the optimal neoadjuvant treatment based on current NCCN guidelines remains unclear as patients with locoregional gastric cancer can either be recommended upfront definitive resection, perioperative chemotherapy, or neoadjuvant chemoradiation.[5] As this has been a source of confusion and debate among gastric cancer providers, randomized controlled trials directly comparing NAC versus NCRT were designed in order to answer this important question;[6–8] however, these trials remain ongoing of which the long-term results remain unknown. In this retrospective cohort study, we identified that perioperative outcomes were largely similar between patients who received NAC and NCRT. However, patients who received NCRT had better histopathologic outcomes. Despite an advantage seen in histopathologic tumor response to NCRT, patients who received NAC alone demonstrated improved survival. Overall, this study contributes important data to the literature in the ongoing discussion of neoadjuvant treatment selection among patients with locoregional gastric cancer.

Although treatment toxicities and postoperative complications are not specifically accounted for within the NCDB, the findings of this study demonstrate largely equivalent safety, using perioperative outcomes as a proxy, between NAC and NCRT. These results are reflective of prior work which fail to demonstrate any differences in specific postoperative complications among patients who received either chemotherapy or chemoradiation prior to surgical resection[15,16] as well as no differences in short-term outcomes such as 30-day mortality, 30-day readmission, and postoperative LOS.[17] Importantly, our data is consistent with the interim results of the TOPGEAR trial as well which identified that administration of NCRT does not significantly increase treatment toxicity or surgical morbidity compared to those who receive NAC alone.[8] However, unlike prior studies comparing neoadjuvant treatments for gastric cancer, we identified that patients who received NCRT had a 10% longer LOS compared to those who received NAC alone. While results from randomized controlled clinical trials are typically largely accrued from highly specialized centers, using a large national database allows for the evaluation of perioperative outcomes among the majority of cancer centers in the US which may be a more accurate reflection of national outcomes in aggregate. Additionally, as the current study uses a more contemporary cohort compared to prior retrospective studies,[17,18] these results may be further representative of more current perioperative outcomes as practice patterns evolve over time. As increasing LOS is associated with more costly and lower quality care,[19] assessing this difference in neoadjuvant treatment selection is an important consideration for gastric cancer providers to be aware of.

The results of this study also demonstrate that pathologic assessment of response to therapy is not always congruent with survival as patients who received NCRT had improved PCR, negative margins, and negative pathologic lymph nodes compared to patients in the NAC cohort yet demonstrated worse survival in comparison. Similar findings have been shown in prior work, showing that patients who receive NCRT are more likely to exhibit improved histopathologic outcomes as opposed to patients who receive NAC alone.[17] However, in this study, we identified that despite the benefit of improved histopathologic outcomes following NCRT, patients who received NAC actually demonstrated improved survival. As long-term survival for patients with gastric cancer is driven by the presence of distant metastases,[20,21] the improved overall survival for patients who received NAC is likely attributable to the delivery of multi-agent systemic chemotherapy. Although patients who received NCRT exhibited better histopathologic outcomes, and thus potentially improved local control of disease, the administration of low dose chemotherapeutic agents for the purposes of radiosensitization, rather than systemic disease control, may be insufficient to offer a comparable benefit in terms of survival. Therefore, these findings highlight that the way response to treatment is currently analyzed warrants further investigation as this may not accurately reflect clinical efficacy. In addition, future work is needed to identify other potential biomarkers of response to treatment which more accurately predict prognosis.

Moreover, the implementation of newer chemotherapeutic regimens following the published results of the FLOT4-AIO trial may have contributed to the survival advantage of patients who received NAC compared to NCRT in this study.[4] Interestingly, previous work by Ikoma et al similarly evaluating NAC versus NCRT found no difference in survival between these two treatment strategies using the NCDB.[17] However, several advances in the form of randomized controlled trials have been made since this study was performed which only includes patients who were diagnosed with gastric cancer through the year 2014. More recently, treatment practices have evolved among gastric cancer providers who now more frequently administer FLOT chemotherapy which has been shown to be superior in terms of patient outcomes compared to the traditional chemotherapeutic regimen of ECF.[4,22] As this study includes a more contemporary cohort, we found contrasting results to previous reports where patients who received NAC actually had improved survival compared to the NCRT group. Although the NCDB does not contain data with regards to specific chemotherapeutic agents administered, we hypothesize that the utilization of modern chemotherapeutic regimens for gastric cancer may contribute to this finding.

Overall, this study has several important clinical implications. As current NCCN guidelines for patients with locoregional gastric cancer remain unclear,[5] additional contributions to the literature are needed to provide further data regarding neoadjuvant treatment selection. As it stands, current guidelines are not clearly defined, given the multiple disparate treatment pathways recommended for this patient population. Thus, until clearly defined, neoadjuvant treatment selection for patients with locoregional gastric cancer remains a critical topic within the field of oncology. The data from our study illustrate the need for randomized controlled trials directly comparing NAC and NCRT among patients with T2-T4 and/or node positive disease. As the TOPGEAR and CRITICS-II trials are currently ongoing, the results of this study provide an important, and updated, contribution to the literature with regards to neoadjuvant treatment selection for gastric cancer.

In addition to the limitations which are similar to those inherent to the use of any large retrospective database, this study is limited by potential selection bias from physician or institutional preferences with the use of one neoadjuvant treatment compared to another. However, propensity score matching was used in an attempt to mitigate this bias in which there were no differences in our results between the unmatched versus matched cohorts. In addition, the NCDB does not include data regarding specific chemotherapeutic regimens. As previously mentioned, the use of certain chemotherapeutic agents has evolved over the past several years with a shift from the use of traditional ECF therapy to now more frequently utilizing FLOT for patients with gastric cancer. Thus, differences in patient outcomes as a result of these different regimens cannot be specifically accounted for. Lastly, the NCDB does not collect data regarding timing and site of disease recurrence, which may help to better understand modality specific disease control. Thus, outcomes such as disease-free survival between NAC versus NCRT could not be included.

Conclusion

Using a large national database, we identified that although there were few differences in perioperative outcomes between different neoadjuvant treatments for gastric cancer, patients who received NCRT had improved histopathologic outcomes compared to those who received NAC alone. Despite this improved histopathologic response to therapy, patients in the NAC cohort exhibited improved survival. These results demonstrate that histologic assessment of treatment response may not accurately reflect clinical efficacy and additionally support the continued need for improved national treatment guidelines following the results of ongoing randomized controlled trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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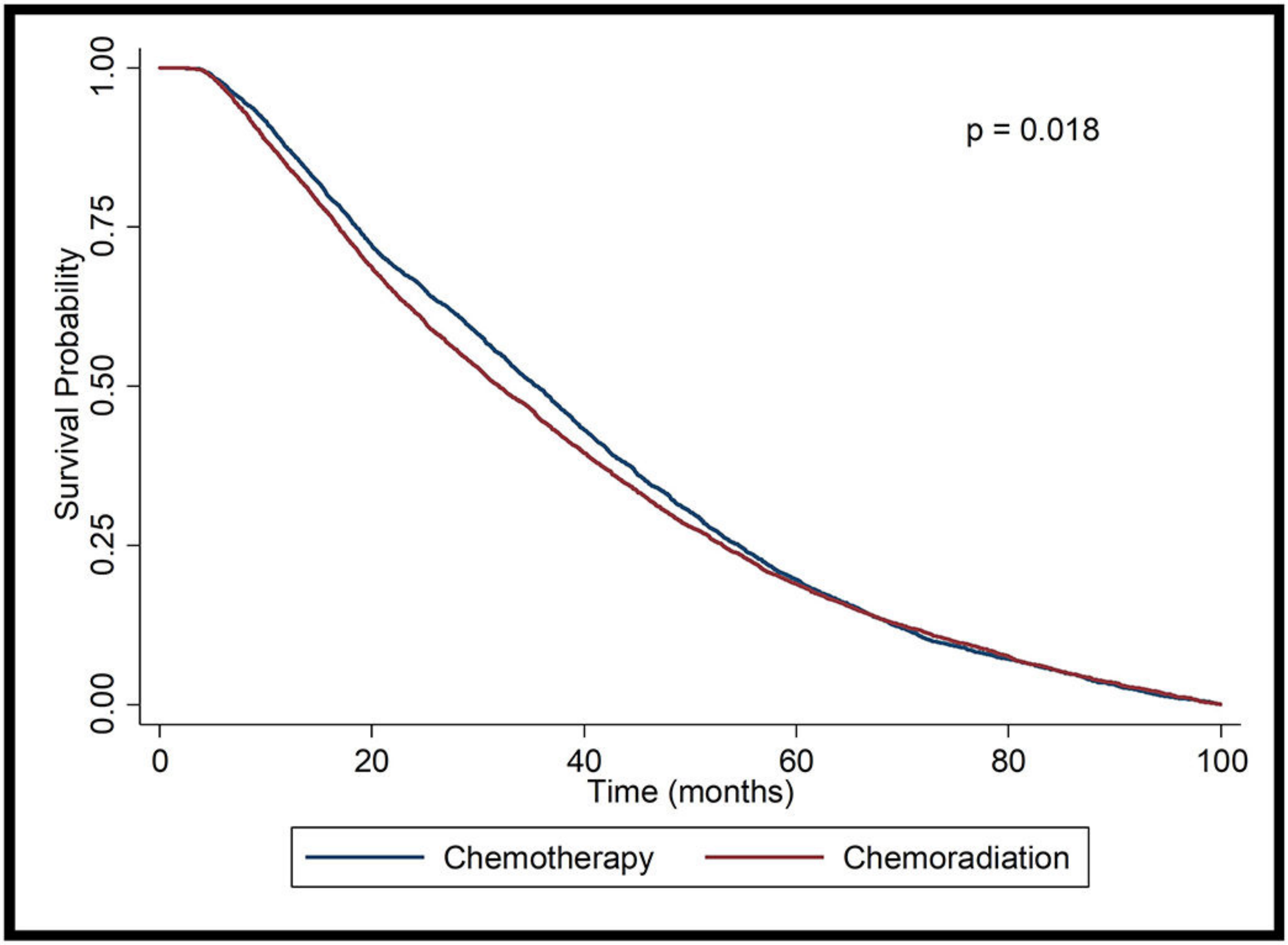
Synopsis

Although perioperative outcomes were similar, neoadjuvant chemoradiation was associated with better tumor response when assessed histologically although neoadjuvant chemotherapy was associated with improved survival. These data demonstrate the importance of systemic control of disease in patients with locoregional gastric cancer.


p = 0.018
Survival Probability
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
100
Time (months)
Chemotherapy
Chemoradiation

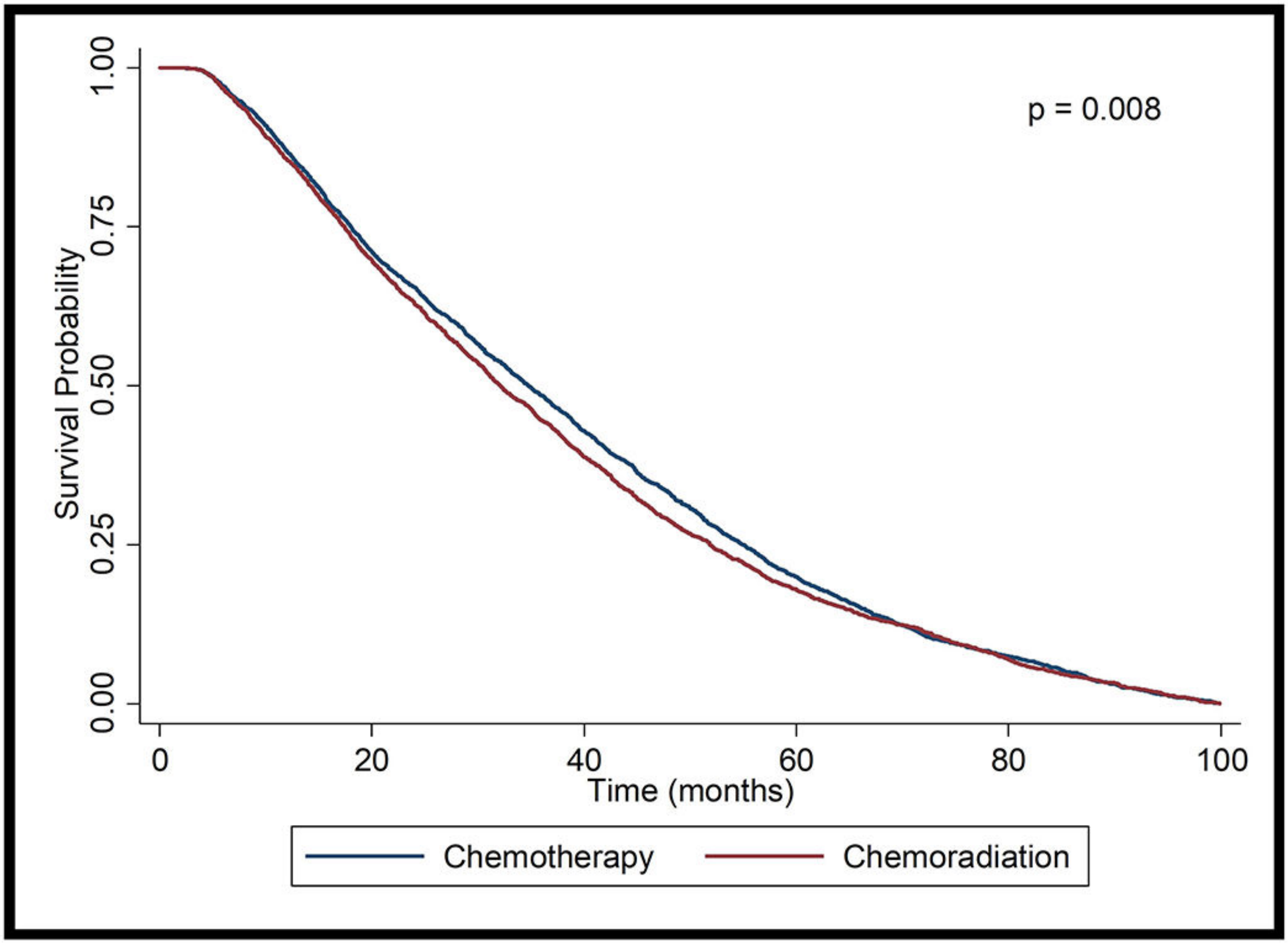


Figure 1:
Kaplan-Meier curves comparing overall survival among patients who received neoadjuvant chemotherapy and chemoradiation for gastric cancer within the a) unmatched, and b) propensity score matched cohort.

Table 1.

Characteristics of patients who received neoadjuvant chemotherapy and chemoradiation followed by surgical resection for gastric cancer.

	Chemotherapy, N (%) (N=4,221, 42.9%)	Chemoradiation, N (%) (N=5,610, 57.1%)	p-value
Gender			<0.001
Male	2,769 (66.2)	4,705 (83.9)	
Female	1,425 (33.8)	905 (16.1)	
Age (years)			<0.001
18-50	569 (13.5)	550 (9.8)	
51-50	1,060 (25.1)	1,512 (27.0)	
61-75	2,106 (49.9)	3,090 (55.1)	
75+	486 (11.5)	458 (8.2)	
Race			<0.001
White	2,451 (58.1)	4,957 (88.4)	
Black	624 (14.8)	200 (3.6)	
Hispanic	552 (13.1)	177 (3.2)	
Asian	423 (10.0)	94 (1.7)	
Other/Unknown	171 (4.1)	182 (3.2)	
Insurance			<0.001
Private	1,892 (44.8)	2,655 (47.3)	
Uninsured	123 (2.9)	99 (1.8)	
Medicaid	353 (8.4)	284 (5.1)	
Medicare	1,795 (42.5)	2,488 (44.4)	
Other Government	58 (1.4)	84 (1.5)	
Facility Type			<0.001
Academic	2,511 (59.5)	3,010 (53.7)	
Community	106 (2.5)	131 (2.3)	
Comprehensive Community Cancer Program	990 (23.5)	1,365 (24.3)	
Integrated Network Cancer Program	614 (14.6)	1,104 (19.7)	
Charlson/Deyo Score			<0.001
0	2,968 (70.3)	3,876 (69.1)	
1	905 (21.4)	1,297 (23.1)	
≥ 2	348 (8.2)	437 (7.8)	
Tumor Location			<0.001
Cardia	1,255 (29.7)	5,305 (94.6)	
Fundus/Body	1,612 (38.2)	177 (3.2)	
Antrum/Pylorus	951 (22.5)	67 (1.2)	
Overlapping	403 (9.6)	61 (1.1)	

	Chemotherapy, N (%) (N=4,221, 42.9%)	Chemoradiation, N (%) (N=5,610, 57.1%)	p-value
Differentiation			<0.001
Well	93 (2.2)	210 (3.7)	
Moderate	908 (21.5)	1,904 (33.9)	
Poor	2,745 (65.0)	2750 (49.0)	
Unknown/Not Reported	475 (11.3)	746 (13.3)	
Lymphovascular Invasion			<0.001
Present	1,317 (31.2)	924 (16.5)	
Absent	1,701 (40.3)	2,706 (48.2)	
Unknown/Not Reported	1,203 (28.5)	1,980 (35.3)	
Tumor Size			<0.001
≤3.0 cm	809 (19.2)	1,329 (23.7)	
>3.0 cm	1,633 (38.7)	1,901 (33.9)	
Unknown/Not Reported	1,779 (42.2)	2,380 (42.4)	
Clinical T-Category [a]			<0.001
T1	118 (2.8)	141 (2.5)	
T2	982 (23.3)	1,088 (19.4)	
T3	2,718 (64.4)	4,230 (75.4)	
T4	403 (9.6)	151 (2.7)	
Clinical N-Category [a]			<0.001
N0	1,807 (42.8)	2,067 (36.8)	
N1	1,793 (42.5)	2,757 (49.1)	
N2	580 (13.7)	784 (14.0)	
N3	41 (1.0)	2 (0.1)	

[a] Clinical stage of disease, including T-Category and N-Category, determined by the American Joint Committee on Cancer staging system.

Table 2.

Unadjusted perioperative and histopathologic outcomes among patients who received neoadjuvant chemotherapy and chemoradiation followed by surgical resection for gastric cancer.

	Unmatched			Matched		
	Chemotherapy, N (%)	**Chemoradiation, N (%)**	**p-value**	**Chemotherapy, N (%)**	**Chemoradiation, N (%)**	**p-value**
Perioperative Outcomes						
30-day Readmission	222 (5.3)	387 (6.9)	0.001	168 (5.7)	206 (7.0)	0.042
30-day Mortality	78 (1.9)	135 (2.4)	0.06	61 (2.1)	84 (2.9)	0.053
90-day Mortality	183 (4.3)	321 (5.7)	0.002	142 (4.8)	172 (5.8)	0.082
Length of Stay, median [IQR]	8 [6-11]	9 [7-13]	<0.001	8 [6-11]	9 [7-13]	<0.001
Histopathologic Outcomes						
Pathologic Complete Response	304 (7.2)	826 (14.7)	<0.001	231 (7.9)	439 (14.9)	<0.001
Negative Margins	3,841 (91.0)	5,264 (95.6)	<0.001	2,670 (90.6)	2,832 (96.1)	<0.001
Negative Pathologic Lymph Nodes	1,928 (45.7)	3,320 (59.2)	<0.001	1,355 (46.0)	1,759 (59.7)	<0.001

Table 3.

Association between neoadjuvant treatment strategies with perioperative and histopathologic outcomes on adjusted multivariable regression models.

	Unmatched	Matched
	Odds Ratio (95% Confidence Interval)	
Perioperative Outcomes		
30-day Readmission [a]		
Neoadjuvant Treatment		
Chemotherapy	1.00 (REF)	1.00 (REF)
Chemoradiation	1.18 (0.89-1.55)	1.21 (0.90-1.62)
30-day Mortality [a]		
Neoadjuvant Treatment		
Chemotherapy	1.00 (REF)	1.00 (REF)
Chemoradiation	1.01 (0.69-1.48)	1.17 (0.75-1.82)
90-day Mortality [a]		
Neoadjuvant Treatment		
Chemotherapy	1.00 (REF)	1.00 (REF)
Chemoradiation	1.16 (0.89-1.52)	1.05 (0.78-1.40)
Length of Stay[a,b]		
Neoadjuvant Treatment		
Chemotherapy	1.00 (REF)	1.00 (REF)
Chemoradiation	1.10 (1.04-1.17)	1.09 (1.03-1.16)
Histopathologic Outcomes		
Pathologic Complete Response [a]		
Neoadjuvant Treatment		
Chemotherapy	1.00 (REF)	1.00 (REF)
Chemoradiation	1.58 (1.28-1.93)	1.48 (1.19-1.85)
Negative Margins [a]		
Neoadjuvant Treatment		
Chemotherapy	1.00 (REF)	1.00 (REF)
Chemoradiation	1.62 (1.24-2.12)	1.74 (1.29-2.35)
Negative Pathologic Lymph Nodes [a]		
Neoadjuvant Treatment		
Chemotherapy	1.00 (REF)	1.00 (REF)
Chemoradiation	1.38 (1.21-1.58)	1.32 (1.13-1.54)

[a]Each outcome modeled separately, adjusting for gender, age, race, insurance status, facility type, Charlson/Deyo score, tumor location, tumor differentiation, lymphovascular invasion, tumor size, clinical T-category, and clinical N-category. Reference category for each model is neoadjuvant chemotherapy.

[b]Length of stay was modeled as a multivariable Poisson regression with results reported as incidence-rate ratios and 95% confidence intervals.

Table 4.

Association between neoadjuvant treatment strategies with overall survival on adjusted cox proportional hazards regression.

	Unmatched	Matched
	Hazard Ratio (95% Confidence Interval)	
Neoadjuvant Treatment [a]		
Chemotherapy	1.00 (REF)	1.00 (REF)
Chemoradiation	1.07 (1.01-1.13)	1.10 (1.03-1.18)

[a]Adjusting for gender, age, race, insurance status, facility type, Charlson/Deyo score, tumor location, tumor differentiation, lymphovascular invasion, tumor size, clinical T-category, and clinical N-category.

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