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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Neoadjuvant Chemotherapy Improves Oncological Outcomes and Long-Term Survival Among Elderly Patients with Locally Advanced Gastric Cancer: A Propensity Score Matched Analysis

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ABSTRACT

Introduction. In the USA, approximately half of newly diagnosed patients with GC are 75 years or older. The objective of the current population-based study was to investigate the impact of neoadjuvant chemotherapy (NAC) on the outcomes of elderly patients with locally advanced GC.

Patients and Methods. Patients aged > 75 years were identified from the National Cancer Database (NCDB). The primary outcome of the study was overall survival (OS). Secondary outcomes included lymph node (LN) harvest, surgical margin status, and 30-day mortality. To minimize the effect of selection bias on the assessed outcome between the two study groups (NAC versus no NAC), propensity score matching (PSM) was performed.

Results. After PSM, a total of 1958 patients were included in both groups. NAC utilization increased from 2013 to 2019 (21% versus 42.7%, $p_{trend} < 0.001$). On pathologic analysis, patients who received NAC were more likely to have ≥ 16 LNs evaluated (NAC 60.1% versus no NAC 55.5%, $p = 0.044$) and negative resection margins (NAC 88.6% versus no NAC 83%, $p = 0.001$). Patients who received NAC were also less likely to experience 30-day mortality following resection (NAC 4.1% versus no NAC 7.1%). Receipt of NAC was associated with improved 1-year (73.9% versus 68.3%), 3-year (48.2% versus 43.5%), and 5-year OS (36.9% versus 30.5%) compared with patients who underwent upfront surgery ($p = 0.01$).

Conclusions. Receipt of NAC was associated with improved oncological outcomes among elderly patients undergoing resection for locally advanced GC.

Keywords Gastric cancer · Elderly · Neoadjuvant chemotherapy · Upfront surgery · Multimodal treatment

Gastric cancer (GC) is the fifth most commonly diagnosed cancer globally,[1] with 5-year overall survival (OS) of less than 40% in Western populations.[2,3] Based on epidemiologic data, an increase in GC incidence is anticipated due to an aging worldwide population.[4] In the USA, approximately half of patients with newly diagnosed GC are 75 years or older.[5] As the population ages, the number of elderly patients undergoing gastrectomy for GC will continue to increase.[6] Over the last decade, improved outcomes in GC treatment have been observed, mainly due to a better understanding of the molecular background of the disease and recent advances in multimodal therapies.[7,8] Nevertheless, strict selection criteria often lead to the exclusion of older patients with GC from clinical trials,[9] mainly due to concerns about the combined effect of aging, comorbidities, and tumor growth.[10,11]

Advances in multimodal treatment have improved the outcomes of patients with GC. Indeed, the addition of perioperative chemo/radiotherapy has been associated with improved OS among patients with resectable GC in the INT-0116

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(chemoradiotherapy after surgery compared with surgery alone) and MAGIC (perioperative chemotherapy versus surgery alone) trials.[12,13] In addition, the FLOT-4 trial demonstrated increased OS among patients with locally advanced GC who received fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT) versus fluorouracil or capecitabine plus cisplatin and epirubicin (ECF/ECX) (50 versus 35 months).[14,15] Nevertheless, median patient age in these trials ranged between 60 and 62 years with the enrollment of elderly individuals (aged 75 years and older) not exceeding 24%. To date, whether receipt of perioperative chemotherapy confers the same survival benefit among elderly patients undergoing resection has not been well studied. While noncompliance with perioperative chemotherapy might negatively affect outcomes, adverse events after neoadjuvant chemotherapy (NAC) may decrease the ability to perform definitive surgery among elderly patients with GC.[16] Therefore, the objective of the current population-based study was to define the impact of NAC on outcomes among elderly patients with locally advanced GC undergoing gastrectomy. In particular, we sought to characterize trends in NAC administration over time at a nationwide level, as well as compare the oncological outcomes of elderly patients undergoing NAC and resection versus upfront resection for locally advanced GC.

PATIENTS AND METHODS

Data Source and Study Design

Patients aged ≥ 75 years with stage II/III GC (cT2–4aN0–3M0) were identified from the National Cancer Database (NCDB) 2019 Participant Use File (PUF).[17] The NCDB is a comprehensive clinical oncology database, which comprises over 34 million individual cancer patient records. The NCDB collects data from over 1500 Commission on Cancer (CoC) accredited medical facilities across the United States. The data repository captures details on more than 70% of index cancer cases on a national scale. The age cut-off of 75 years was based on the National Institute on Aging definition of "older age."[18] GC diagnosis was based on the International Classification of Disease for Oncology, third edition (ICD-0-3) histology codes.[19] Surgical Procedures of Primary Site codes (30–80) were used to identify gastrectomy surgical procedures. Clinical disease stage II and III were classified according to the appropriate edition of the American Joint Committee of Cancer (AJCC) staging system based on year of diagnosis.[20] To control for potential historical bias, only data from the last 7 years (2013–2019) were analyzed. Patients without adenocarcinoma, who did not undergo resection, had early (cT1) or metastatic (cM1) GC, underwent palliative care, or died before planned curative-intent treatment were excluded. The study was determined to be exempt by the Institutional Review Board of the Ohio State University Wexner Medical Center.

Variables and Outcomes

Sociodemographic and clinicopathologic data were collected on age, sex, race, facility academic affiliation, facility location, median household income, education level, type of insurance, clinical stage, and Charlson comorbidity index (CCI). The primary outcome was OS, defined as the time elapsed between gastrectomy and death or last follow-up. The secondary outcome was lymph node (LN) harvest, surgical margin status, prolonged length of hospital stay (LOS, defined as exceeding the 75th percentile, as previously reported[21]), 30-day readmission, and 30-day mortality.

Statistical Analyses

Descriptive statistics were presented as median [interquartile range (IQR)] and frequency (%) for continuous and categorical variables, respectively. Bivariate analyses included the Wilcoxon rank-sum test for continuous variables and chi-square test or Fisher's exact test for categorical variables, as appropriate. The trend of NAC for elderly patients with locally advanced GC was assessed using the Mantel–Haenszel trend test. Survival probabilities were estimated using Kaplan–Meier analysis and compared using the log-rank test. To minimize the effect of selection bias of measured covariates on the assessed outcome between the two study groups (NAC versus no NAC), propensity score matching (PSM) was performed. A propensity score was calculated for each patient using a logistic regression model, which was fitted for type of treatment using preoperative variables including age, sex, race, CCI, median income, education attainment, insurance status, rurality, facility type, and clinical stage. Nearest neighbor 1:1 matching without replacement was employed by utilizing a caliper of 0.20. Results relative to covariate subgroups were presented as standardized mean differences (SMDs). SMDs below 0.1 signified minimal disparities between means.[22] Statistical significance was assessed at $\alpha = 0.05$. All statistical analyses were performed using R version 4.2.0 (R Project for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

A total of 3595 patients who underwent curative-intent treatment for locally advanced GC were included in the final analytic cohort. Most patients were male (n = 2304, 64.2%) and white (n = 2685, 74.7%). The median age at the time of diagnosis was 80 years (IQR 7884).

Approximately one-half of patients were diagnosed with clinical stage II disease (*n* = 1697, 47.2%), while the remaining individuals presented with clinical stage III (*n* = 1898, 52.8%) GC. The majority of individuals had a CCI of 0 (*n* = 2271, 61.7%) and were treated at a nonacademic facility (*n* = 2257, 62.8%) in a metropolitan area (*n* = 3057, 85%) (Table 1; Supplementary Table 1).

Among the entire cohort, 2519 (70.1%) patients underwent upfront surgery (no NAC group), while 1076 (29.9%) received preoperative chemotherapy (NAC group). Of note, patients receiving NAC were younger (NAC 78 years, IQR 77–81 versus no NAC 81 years, IQR 78–85), more frequently were male (NAC 74.4% versus no NAC 59.8%) and had a lower CCI (CCI 0: NAC 65.8% versus no NAC 59.9%) (Fig. 1). In addition, individuals receiving NAC more

TABLE 1 Baseline characteristics of study cohort relative to the receipt of neoadjuvant chemotherapy among elderly patients with locally advanced gastric cancer

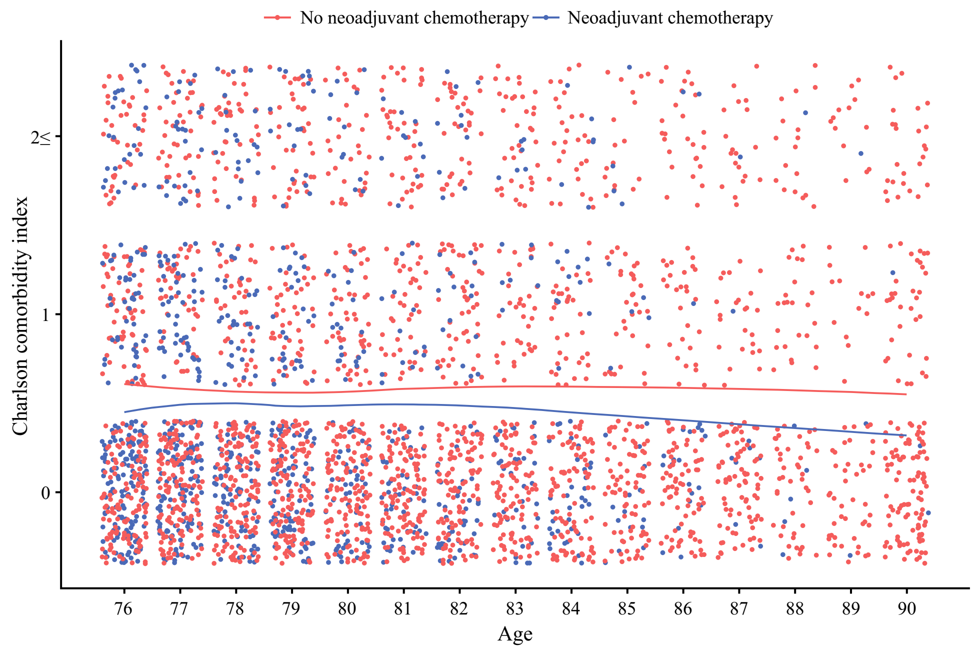
Variables	Before PSM		SMD	After PSM		SMD
	No NAC *n* = 2597	NAC *n* = 1076		No NAC *n* = 979	NAC *n* = 979	
	n (%)	*n* (%)		*n* (%)	*n* (%)	
Age*	81.00 [78.00, 85.00]	78.00 [77.00, 81.00]	**0.735**	79.00 [77.00, 81.00]	79.00 [77.00, 81.00]	0.015
Gender						
Female	1012 (40.2)	275 (25.6)		266 (27.2)	270 (27.6)	
Male	1507 (59.8)	801 (74.4)	**0.315**	713 (72.8)	709 (72.4)	0.009
Race						
White	1788 (71.0)	897 (83.4)	**0.311**	795 (81.2)	801 (81.8)	0.047
Black	390 (15.5)	78 (7.2)		90 (9.2)	78 (8.0)	
Other	341 (13.5)	101 (9.4)		94 (9.6)	100 (10.2)	
Charlson comorbidity index						
0	1509 (59.9)	708 (65.8)	**0.144**	639 (65.3)	634 (64.8)	0.011
1	564 (22.4)	228 (21.2)		206 (21.0)	208 (21.2)	
≥ 2	446 (17.7)	140 (13.0)		134 (13.7)	137 (14.0)	
Median household income						
< $48,000	936 (37.2)	277 (25.7)	**0.251**	294 (30.0)	271 (27.7)	0.052
≥ $48,000	1295 (51.4)	638 (59.3)		548 (56.0)	565 (57.7)	
Unknown	288 (11.4)	161 (15.0)		137 (14.0)	143 (14.6)	
Education attainment, no HSD						
> 10.9%	1015 (40.3)	544 (50.6)	**0.298**	468 (47.8)	478 (48.8)	0.04
< 10.8%	1199 (47.6)	357 (33.2)		364 (37.2)	346 (35.3)	
Unknown	305 (12.1)	175 (16.3)		147 (15.0)	155 (15.8)	
Insurance						
Uninsured/other	66 (2.6)	35 (3.3)	0.096	30 (3.1)	31 (3.2)	0.007
Private	206 (8.2)	115 (10.7)		101 (10.3)	100 (10.2)	
Public	2247 (89.2)	926 (86.1)		848 (86.6)	848 (86.6)	
Rurality						
Nonmetropolitan	295 (11.7)	139 (12.9)	0.066	127 (13.0)	129 (13.2)	0.013
Metropolitan	2158 (85.7)	899 (83.6)		820 (83.8)	816 (83.4)	
Unknown	66 (2.6)	38 (3.5)		32 (3.3)	34 (3.5)	
Facility type						
Nonacademic	1681 (66.7)	576 (53.5)	**0.272**	551 (56.3)	554 (56.6)	0.006
Academic	838 (33.3)	500 (46.5)		428 (43.7)	425 (43.4)	
Stage						
II	1167 (46.3)	530 (49.3)	0.059	479 (48.9)	468 (47.8)	0.022
III	1352 (53.7)	546 (50.7)		500 (51.1)	511 (52.2)	

* presented as median [IQR]

Bold font signifies significant difference

PSM propensity score matching, *NAC* neoadjuvant chemotherapy, *HSD* high school diploma, *SMD* standardized mean difference

FIG. 1 Scatter plot showing the distribution of patient age and Charlson comorbidity index relative to the receipt of neoadjuvant chemotherapy

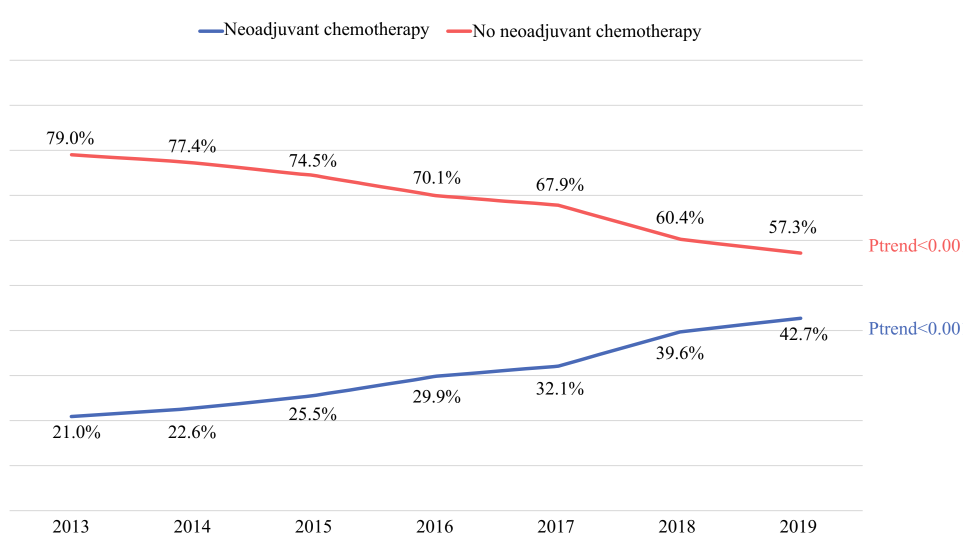


frequently had private insurance (NAC 10.7% versus no NAC 8.2%) and higher income (median household income ≥ $48,000; NAC 59.3% versus no NAC 51.4%) compared with individuals undergoing upfront resection (Table 1). Patients receiving NAC were more frequently treated at academic centers compared with individuals receiving upfront resection (NAC 46.5% versus no NAC 33.3%), whereas disease stage was not associated with receipt of NAC (stage III, NAC versus no NAC, 50.7% versus 53.7%) (Table 1).

Trends of NAC Administration

An increasing trend in NAC receipt was observed over the study period examined. Of note, use of NAC almost doubled by the end of the study period (2013 21.0% versus 2019 42.7%, $p_{trend} < 0.001$) (Fig. 1). In addition, while most elderly patients underwent upfront surgery in 2013 (NAC 21.0% versus no NAC 79.0%), the proportion of patients receiving NAC versus upfront surgery was almost comparable in 2019 (NAC 42.7% versus no NAC 57.3%). When examining the type of systemic therapy administered, an increasing trend in receipt of multiagent NAC was observed (2013 37.0% versus 2019 58.0 %, $p_{trend} < 0.001$), whereas a decreasing trend in receipt of single-agent NAC (2013 21.0% versus 2019 13.0 %, $p_{trend} = 0.05$) and NAC omission (2013 42.0% versus 2019 29.0%, $p_{trend} = 0.012$) was observed over the same time period (Figs. 2, 3).

FIG. 2 Trends in receipt of neoadjuvant chemotherapy among elderly patients with locally advanced gastric cancer over the study period (2013–2019)



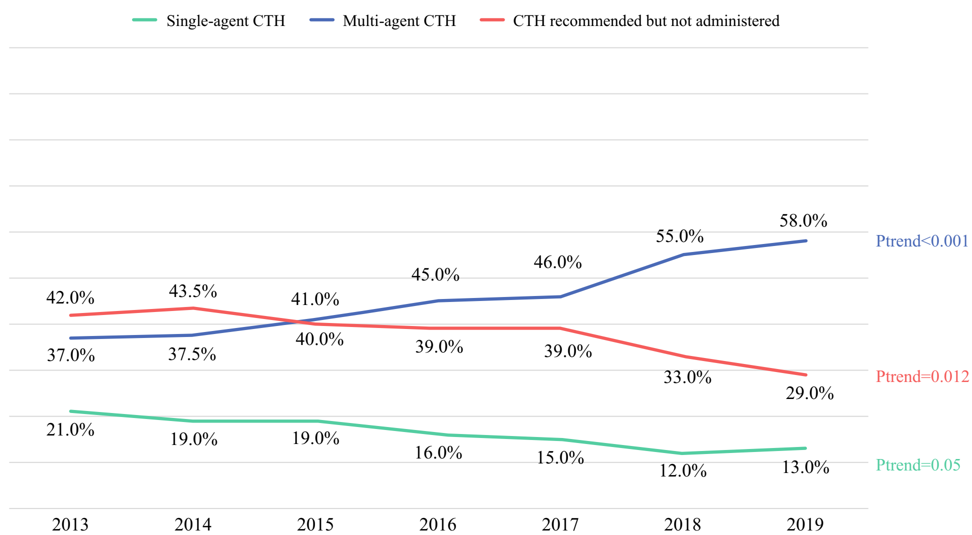


FIG. 3 Trends in type of neoadjuvant chemotherapy regimen over the study period (2013–2019)

Short- and Long-Term Outcomes Relative to the Receipt of NAC before and after PSM

In the overall cohort, patients who received NAC were more likely to have lymphadenectomy with adequate LN harvest (NAC 59.8% versus no NAC 53.9%, $p = 0.001$) and negative surgical margins (NAC 88.9% versus no NAC 83.0%, $p < 0.001$), as well as lower 30-day readmission (NAC 5.4% versus no NAC 7.3%, $p = 0.047$) and lower 30-day mortality (NAC 4.2% versus no NAC 8.6%, $p < 0.001$) compared with individuals undergoing upfront surgery (Supplementary Table 2). In addition, patients who received NAC prior to resection had improved long-term survival versus individuals undergoing upfront surgery for locally advanced GC (5-year OS 37.4% versus 26.3%, $p < 0.001$, Supplementary Fig. 1).

After PSM, a total of 979 patients were included in both NAC and no NAC groups. The two groups were well balanced with no significant differences in baseline characteristics (SMDs < 0.10) (Table 1). Of note, in the PSM cohort, patients who received NAC followed by gastrectomy had a higher likelihood of adequate LN harvest, negative resection margins, and lower chance of 30-day mortality versus individuals undergoing upfront surgery for locally advanced GC (all $p < 0.05$; Table 2). Of note, while the number of LN harvested decreased with age in the upfront resection group, the average number of LNs harvested increased with age among the NAC plus resection group (Fig. 4). No difference in 30-day readmission and/or prolonged LOS was observed between the PSM NAC and no NAC groups.

In assessing the PSM cohort, median and 5-year OS were 30.5 months and 33.7%, respectively. Of note, NAC receipt was associated with improved 1-, 3-, and 5-year OS compared with upfront surgery (1-, 3-, and 5-year OS, NAC 73.9%, 48.2%, 36.9% versus no NAC 68.3%, 43.5%, and 30.5%, $p = 0.01$, Fig. 5).

TABLE 2 Short-term outcomes relative to the use of neoadjuvant chemotherapy after propensity score matching

Variables	No NAC *n* = 979 *n* (%)	NAC *n* = 979 *n* (%)	*p*-Value
Lymph nodes retrieved			
< 16	436 (44.5)	391 (39.9)	**0.044**
≥ 16	543 (55.5)	588 (60.1)	
Surgical margin			
Positive	166 (17.0)	112 (11.4)	**0.001**
Negative	813 (83.0)	867 (88.6)	
Prolonged length of stay			
Yes	222 (24.9)	215 (24.5)	0.899
No	670 (75.1)	662 (75.5)	
30-day readmission			
Yes	68 (6.9)	52 (5.3)	0.158
No	911 (93.1)	927 (94.7)	
30-day mortality			
Yes	64 (7.1)	33 (4.1)	**0.011**
No	833 (92.9)	764 (95.9)	

Bold font signifies significance

NAC neoadjuvant chemotherapy

DISCUSSION

A 70% increase in cancer incidence among older adults is expected by 2030, with the most significant increase expected for tumors associated with high mortality rates including GC.[4] Prior research has demonstrated marked age disparities among participants in cancer clinical trials,[23]

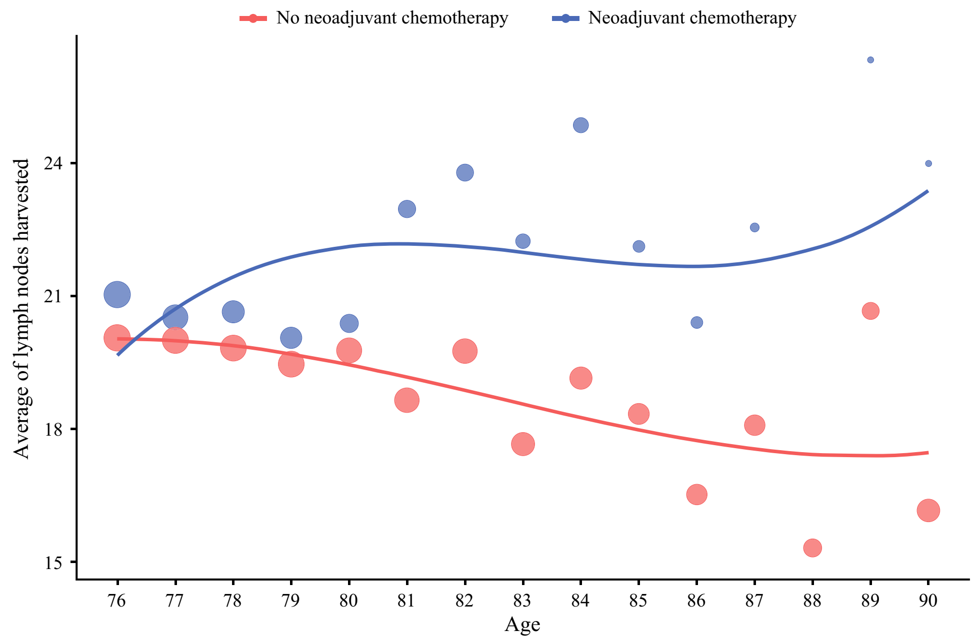


FIG. 4 Association of patient age with average number of LNs harvested relative to the receipt of neoadjuvant chemotherapy

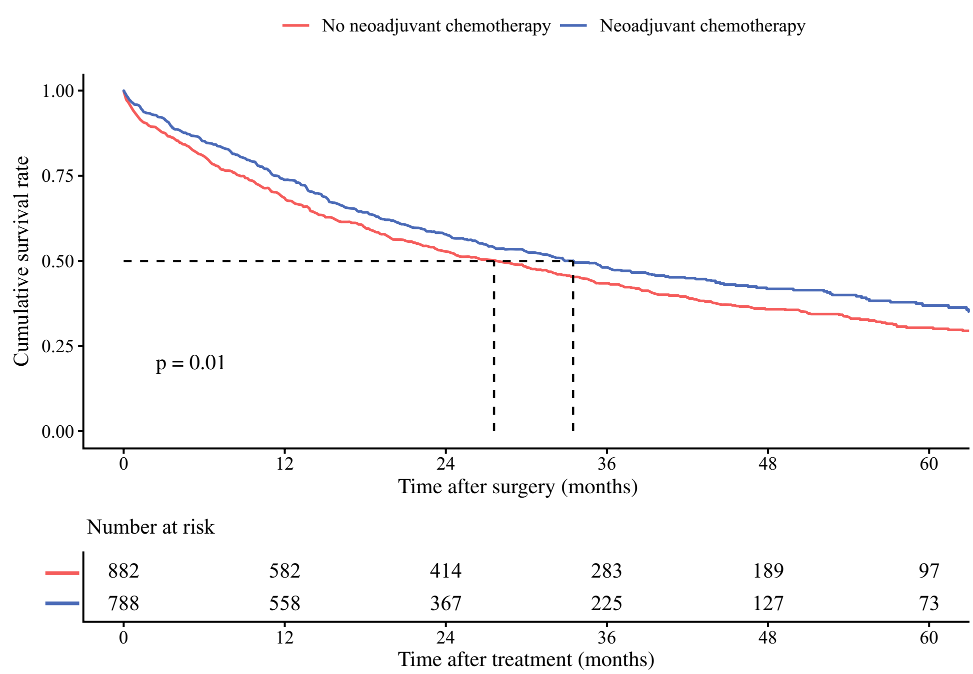


FIG 5 Kaplan–Meier curve demonstrating differences in overall survival among elderly patients undergoing NAC + resection versus upfront resection for locally advanced gastric cancer after propensity score matching

suggesting that clinical trial data may not be representative of the entire spectrum of elderly patients.[24] Currently, the gold standard treatment for locally advanced GC includes preoperative chemotherapy followed by curative-intent resection. This treatment approach may create difficulties in elderly patients due to this patient population having a higher prevalence of frailty and significant comorbidities that may prevent initiation/completion of multimodal treatment strategies.[25] The current study was important because we assessed the trends and the impact of NAC on short- and long-term outcomes among elderly patients undergoing gastrectomy for locally advanced GC at a nationwide level. Of note, the utilization of NAC administration doubled from 2013 to 2019. Factors associated with NAC administration included younger age, lower CCI, higher education, and household income, as well as the type of the facility at which the patient received treatment. After PSM, patients who received NAC followed by gastrectomy for locally advanced GC had higher likelihood of adequate LN harvest, negative resection margins, and lower 30-day mortality compared with individuals undergoing upfront surgery. Receipt of NAC followed by gastrectomy was associated with improved long-term survival compared with upfront resection among both the crude, as well as the PSM cohorts.

According to the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) guidelines, NAC followed by resection should be considered the recommended treatment of locally advanced GC.[7,26] While gastrectomy remains the mainstay of treatment in nonmetastatic disease, NAC allows for primary tumor downstaging and may contribute to the clearance of clinically occult nodal- and micrometastases, ultimately increasing negative margin resection following gastrectomy.[27] In line with previous literature, the current study demonstrated an increasing trend in NAC utilization among elderly patients with locally advanced GC over time. Specifically, utilization of NAC doubled from 2013 to 2019 with concurrent changes over time in the type of NAC regimen administered. For example, while only 37% of individuals received multiagent NAC in 2013, the respective figure reached up to 58% in 2019 ($p < 0.001$). In contrast, there was a decreasing trend over time in the use of single-agent NAC, as well as a lower number of patients who had NAC omitted as part of their therapeutic plan (Fig. 3). Although the exact type of NAC regimen used could not be assessed due to the limitations of the NCDB, the increased use of multi- rather than single-agent chemotherapy may have contributed to more favorable outcomes in the NAC group. Specifically, the FLOT4 trial reported a survival benefit associated with docetaxel-based triplet perioperative compared with ECF regimen among elderly patients with GC.[15]

Previous studies have noted marked disparities relative to the utilization of preoperative systemic treatment for locally advanced GC in the USA.[28] In fact, less than one-third of patients with stage II/III GC received the recommended NAC, of which the majority were younger patients with lower CCI and had more favorable socioeconomic status.[28] In line with these data, the current study noted NAC utilization among approximately 30% of elderly patients with locally advanced GC. Of note, patients who received NAC were younger, more frequently were white, had a lower CCI, a higher education, and a higher median income compared with individuals who underwent upfront resection for locally advanced GC. These data were in line with results from the Netherlands, which demonstrated that individuals aged ≥ 75 years who received NAC were younger and had fewer comorbidities versus individuals undergoing upfront resection for GC.[9] Apart from patient age and performance status, [29–31] the current study served to highlight how socioeconomic disparities impacted receipt of NAC for GC. In particular, NAC utilization was not only dependent on chronological age and overall patient health status, but also disparities relative to race/ethnicity, education, and income. In turn, strategies to mitigate these disparities should be employed at a nationwide level to ensure equal access to multi-modal care.

According to NCCN recommendations, patients with positive resection margins after gastrectomy for GC should receive postoperative fluoropyrimidine-based chemoradiation.[7] From an oncological perspective, NAC may increase likelihood of a margin negative resection and be better tolerated than adjuvant chemo(radio)therapy, particularly in older patients.[26,32] Results of CRITICS trial demonstrated comparable OS and progression-free survival among patients undergoing NAC followed by gastrectomy, regardless of receipt of adjuvant chemoradiotherapy or chemotherapy alone.[33] The current study demonstrated that receipt of NAC was associated with a higher likelihood of an R0 resection, as well as higher chance of adequate lymphadenectomy (LN ≥ 16) at time of gastrectomy for locally advanced GC. In turn, adequate LN harvest is imperative to stage the disease appropriately and helps more accurately stratify patients relative to long-term prognosis.[34] Of note, patients undergoing NAC followed by resection had improved long-term outcomes compared with individuals undergoing upfront resection, which was consistent both in the crude cohort as well as after PSM. In contrast, a previous study from the Netherlands had failed to demonstrate a survival benefit of NAC among patients aged ≥ 75 years with GC.[9] Though the explanation for the difference in findings may be multifactorial, the higher incidence of negative margin resection and improved LN harvest in the NAC group likely contributed to differences in survival. In the current study, receipt of NAC plus gastrectomy was associated with lower 30-day mortality versus upfront resection, suggesting that preoperative systemic treatment allowed for the selection of patients who were fit for surgery (i.e., responded to NAC and had appropriate performance status to tolerate surgery). In turn, NAC may provide a means to treat systemic micrometastatic disease and cytoreduce the primary tumor, as well as provide a test of cancer biology and overall patient physiology.

The results of the current study need to be interpreted in light of certain limitations. Due to the retrospective nature of the study, selection bias was possible since an intention-to-treat analysis was not feasible. PSM was used, however, to mitigate any possible confounding due to measured variables. Also, owing to the limitations of the NCDB, certain variables could not be assessed including Lauren histological subtype and tumor regression grade. In addition, data on complications were not available in NCDB; however, LOS was used as a surrogate for severe complications. While type of NAC (i.e., single versus multiagent) could be generally assessed, data on the exact chemotherapy regimen were not available for further analysis.

In conclusion, an increasing trend in NAC use was noted among elderly patients with locally advanced GC undergoing gastrectomy in the USA. Marked differences in NAC utilization were noted relative to patient age, CCI, education, income, and facility type. Receipt of NAC was associated with higher likelihood of an adequate LN harvest, negative resection margin status, as well as improved long-term survival compared with upfront resection for locally advanced GC. Multimodal treatment of GC should be strongly considered as the treatment of choice even among elderly patients.

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