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National Underutilization of Neoadjuvant Chemotherapy for Gastric Cancer

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Abstract

Background Since the publication of the landmark MAGIC trial in 2006, neoadjuvant chemotherapy has become the standard of care for stage II/III gastric cancer. Nevertheless, many patients still do not begin their treatment with neoadjuvant chemotherapy. The objective of our study was to identify factors associated with underutilization of neoadjuvant chemotherapy for stage II/III gastric cancer.

Methods Patients with pathological stage II and III primary gastric cancer between 2004 and 2015 were identified from the American College of Surgeons National Cancer Database. Patients who received neoadjuvant chemotherapy were compared with those who underwent surgery only or surgery followed by chemotherapy. Predictors of receipt of neoadjuvant chemotherapy were identified using multivariable logistic regression model. Median survival was calculated for each treatment strategy.

Results We included 15,947 patients with pathological stage II/III gastric cancer. The proportion of patients receiving neoadjuvant chemotherapy increased from less than 5% before 2006 to 27.5% in 2015. On multivariable analysis, factors associated with no receipt of neoadjuvant therapy included treatment year before 2006 and age greater than 80. Treatment at high-volume centers, academic research programs, or integrated network cancer programs and undergoing total/subtotal or en bloc gastrectomy predicted receipt of neoadjuvant chemotherapy.

Conclusions Ten years after the publication of the MAGIC trial, fewer than 1/3 of patients with stage II/III gastric cancer are receiving neoadjuvant chemotherapy, which has been shown to improve disease-specific survival. Further studies are needed to understand these disparities and ensure both patients and providers are having evidence-based discussions about multimodal therapy for gastric cancer.

Keywords Gastric cancer · Neoadjuvant chemotherapy · Multimodal treatment · Healthcare disparities · Surgical oncology

Introduction

Gastric cancer remains the fourth most common cancer worldwide.[1] While its incidence has decreased in recent years, it still remains the second most deadly cancer worldwide.[2] Unfortunately, gastric cancer has a low rate of early diagnosis. In the USA where there is no regular screening for gastric cancer, it often goes undiagnosed until advanced stages, when symptoms typically manifest.[3] As a result, more than 50% of patients are found to have advanced disease at diagnosis.[4] While five-year survival has increased from less than 15% in the 1970s, it is still estimated to be less than 30% in the USA.[5,6]

Guideline recommended treatment for gastric cancer is dependent on stage of disease. Surgery remains the main tenant for stage 1 gastric cancer. For locally advanced, or regional, gastric cancer, multimodality treatment consisting of surgery,

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chemotherapy, and potentially radiation therapy is recommended. In 2006, the landmark Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial was published, advocating for the use of perioperative chemotherapy (epirubicin, cisplatin, and 5-fluorouracil [ECF]) and surgery for the treatment of stage II or higher gastric cancer, which demonstrated a significantly improved progression-free survival benefit.[7] Since then, multiple phase III trials have also shown the survival benefits of perioperative ECF in multimodal treatment for gastric cancer.[8] In 2017, a multicenter, randomized phase III trial comparing perioperative ECF with the docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) regimen demonstrated improved outcomes with the use of FLOT.[9, 10] Thus, perioperative chemotherapy and surgery is considered the standard of care for the treatment of locally advanced gastric cancer.

Nevertheless, despite high-level evidence demonstrating this survival benefit, there appears to be an underutilization of multimodal therapies, especially neoadjuvant chemotherapy.[11–13] While studies have shown an increase in the use of neoadjuvant systemic therapy after the publication of the MAGIC trial, the most common treatment modality for locally advanced gastric cancer still remains surgery alone.[11–13] Presently, more than 10 years after the landmark MAGIC trial, it still remains unclear what percentage of patients with stage II or higher gastric cancer are receiving neoadjuvant chemotherapy and surgery.

The objective of our study was to determine recent trends in utilization of different therapies for locally advanced gastric cancer. We also sought to identify factors associated with underutilization of neoadjuvant chemotherapy and surgery for locally advanced gastric cancer.

Methods

Data Source and Study Population

Data from the National Cancer Database (NCDB) from 2004 to 2015 were utilized for this study. Established in 1989, the NCDB is a nationwide clinical oncology database sponsored by American College of Surgeons and American Cancer Society. The NCDB offers a nationally representative sample – it includes data collected from more than 1500 accredited facilities in the USA and Puerto Rico, representing more than 70% of newly diagnosed cancer cases in the US – from which to identify existing national practice patterns for cancer treatment, explore cancer care trends, and to improve cancer outcomes.[14] All NCDB data are de-identified,[15] therefore this study was deemed exempt from the University of Wisconsin Institutional Review Board (IRB) approval process.

We included all adult patients (≥ 18 years old) pathologically diagnosed with stage II or stage III (as per 2010 American Joint Committee on Cancer [AJCC] staging guidelines[16]) primary gastric adenocarcinoma. Sequence number – indicating the sequence of malignant and non-malignant neoplasms over the lifetime of the patient – was used to exclude participants with any primary cancer diagnosis other than gastric cancer. NCDB histology codes were used to identify patients with adenocarcinoma. Patients with gastroesophageal (GE) junction tumors were excluded using NCDB topography codes (C161-C169). Patients were divided into groups based on treatment strategy: those who were treated with surgery alone ("surgery only"), those who underwent surgery followed by chemotherapy ("surgery-chemotherapy"), and those who received chemotherapy followed by surgery ("chemotherapy-surgery"). No patients in the "surgery only" group received radiation, but patients in the "chemotherapy-surgery" and "surgery-chemotherapy" groups may have received radiation. A limitation of NCDB data is that we were unable to specifically identify receipt of perioperative chemotherapy; the database only allows for differentiation between preoperative and postoperative chemotherapy. Based on the assumption that patients who received neoadjuvant chemotherapy would continue on to receive postoperative chemotherapy, we considered neoadjuvant chemotherapy ("chemotherapy-surgery") as perioperative chemotherapy.

Study Variables

Patients were divided into 2 groups: those who received chemotherapy-surgery and those who received other treatments (either surgery only or surgery-chemotherapy). Baseline demographic and clinical characteristics of patients who received chemotherapy-surgery were compared with those who received other treatments. These characteristics included year of diagnosis (2004–2006, 2007–2009, 2010–2012, 2013–2015), age (18–58, 59–70, 71–79, ≥ 80 years old), sex (female or male), race (White, Black, Asian/Pacific Island, or other), ethnicity (Spanish/Hispanic), Charlson comorbidity index (0, 1, or ≥ 2), education level (lower than high school education grouped into 4 categories: ≥ 21%, 13–20.9%, 7–12.9%, or < 7%), income (< $38,000, $38,000–$47,999, $48,000–$62,999, or ≥ $63,000), insurance (insured [includes private insurance/managed care, Medicaid, Medicare, or other government insurance], uninsured, or unspecified), primary site of the cancer (identified using ICS-O codes: pylorus/gastric antrum, body, fundus, or not otherwise specified [NOS]), stage (stage II or stage III), surgical procedure of primary site (partial gastrectomy, total/subtotal gastrectomy, en bloc gastrectomy, or other), distance from treatment center (distance in miles between the patient's residence and the hospital that reported the case), hospital volume (calculated by the number of times a particular hospital appeared in the analytical cohort [grouped by quartiles]), and facility type (community cancer program, comprehensive

Table 1 Demographic and clinical characteristics of primary gastric cancer patients (pathological stage II/III) between 2004 and 2015

Characteristics	Total (N = 15,947)	Surgery only or surgery-chemotherapy (N = 13,448)	Chemotherapy-surgery (N = 2499)	p value
Year of diagnosis (N, %)				*< 0.001*
• 2004–2006	3534 (22.16)	3420 (27.45)	114 (6.14)	
• 2007–2009	3353 (21.03)	3052 (22.69)	301 (12.04)	
• 2010–2012	4532 (28.42)	3684 (27.39)	848 (33.93)	
• 2013–2015	4528 (28.39)	3292 (24.48)	1236 (49.46)	
Age categories (N, %)				*< 0.001*
• 18–58	4675 (29.32)	3658 (27.20)	1017 (40.70)	
• 59–70	4597 (28.83)	3693 (27.46)	904 (36.17)	
• 71–79	3885 (24.36)	3403 (25.30)	482 (19.29)	
• 80+	2790 (17.50)	2694 (20.03)	96 (3.84)	
• Female (vs. male) (N, %)	6834 (42.85)	5787 (43.03)	1047 (41.90)	0.292
Race (N, %)				*< 0.001*
• White	10,225 (64.12)	8573 (63.75)	1652 (66.11)	
• Black	3437 (21.55)	2924 (21.74)	513 (20.53)	
• Asian/Pacific Island	1762 (11.05)	1535 (11.41)	227 (9.08)	
• Other/unknown	523 (3.28)	416 (3.09)	107 (4.28)	
• Spanish or Hispanic (N, %)	2278 (15.03)	1866 (14.66)	412 (17.00)	*0.003*
Comorbidity (N, %)				*< 0.001*
• Score 0	10,880 (68.23)	9012 (67.01)	1868 (74.75)	
• Score 1	3730 (23.39)	3221 (23.95)	509 (20.37)	
• Score ≥ 2	1337 (8.38)	1215 (9.03)	122 (4.88)	
Education 2008–2012 (not high school graduate) (N, %)				*< 0.001*
• 21% or more	3975 (25.32)	3413 (25.81)	562 (22.73)	
• 13–20.9%	4402 (28.05)	3758 (28.42)	644 (26.05)	
• 7–12.9%	4478 (28.53)	3755 (28.40)	723 (29.25)	
• Less than 7%	2841 (18.10)	2298 (17.38)	543 (21.97)	
Income 2008–2012 (N, %)				*< 0.001*
• Less than $38,000	3581 (22.82)	3081 (23.31)	500 (20.23)	
• $38,000–$47,999	3520 (22.43)	2999 (22.69)	521 (21.08)	
• $48,000–$62,999	3980 (25.36)	3336 (25.23)	644 (26.06)	
• $63,000+	4610 (29.38)	3804 (28.77)	806 (32.62)	
Insurance (N, %)				0.087
• Not insured	772 (4.84)	635 (4.72)	137 (5.48)	
• Insured	14,821 (92.94)	12,504 (92.98)	2317 (92.72)	
• Unknown	354 (2.22)	309 (2.30)	45 (1.80)	
Primary site (N, %)				*< 0.001*
• Pylorus and Gastric Antrim	6927 (37.17)	5188 (38.58)	739 (29.57)	
• Fundus	715 (4.48)	548 (4.07)	167 (6.68)	
• Body	1781 (11.17)	1449 (10.77)	332 (13.29)	
• NOS	7524 (47.18)	6263 (46.57)	1261 (50.46)	
• Stage III (vs. stage II) (N, %)	9251 (58.01)	7870 (58.52)	1381 (55.26)	*0.002*
Surgical procedure of primary site				*< 0.001*
• Partial gastrectomy	10,178 (63.82)	9046 (67.27)	1132 (45.30)	
• Total/subtotal gastrectomy	3449 (21.63)	2578 (19.17)	871 (34.85)	
• En bloc gastrectomy	1894 (11.88)	1487 (11.06)	407 (16.29)	
• Others	426 (2.67)	337 (2.51)	89 (3.56)	
• Great Circle Distance (mean, SD, miles)	27.0 (105.2)	23.9 (87.2)	43.1 (170.9)	*< 0.001*
Hospital volume				*< 0.001*
• Quartile 1[1, 11] – mean 6.98	4022 (25.22)	3014 (23.17)	338 (14.21)	
• Quartile 2 [11, 22] – mean 16.51	4233 (26.54)	3523 (27.09)	527 (22.15)	

Table 1 (continued)

Characteristics	Total (N = 15,947)	Surgery only or surgery-chemotherapy (N = 13,448)	Chemotherapy-surgery (N = 2499)	p value
• Quartile 3 [22, 39] – mean 29.97	3848 (24.13)	3409 (26.21)	684 (28.75)	
• Quartile 4 [39, 273] – mean 74.81	3844 (24.10)	3061 (23.53)	830 (34.89)	
Facility type (N, %)				*< 0.001*
• Community Cancer Program	1432 (9.33)	1319 (10.15)	113 (4.81)	
• Comprehensive Community Cancer Program	6019 (39.22)	5354 (41.20)	665 (28.30)	
• Academic/Research Program	6141 (40.02)	4838 (37.23)	1303 (55.45)	
• Integrated Network Cancer Program	1754 (11.43)	1485 (11.43)	269 (11.45)	

community cancer program, academic/research program, or integrated network cancer program).

Statistical Analysis

Baseline demographic and clinical characteristics were compared between chemotherapy-surgery patients and those who received other treatments (surgery only and surgery-chemotherapy) using Pearson's χ^2-test for categorical variables and Student's t test for continuous variables.

Multivariable logistic regression was used to identify factors associated with lack of receipt of chemotherapy-surgery among primary gastric cancer patients. The logistic regression model for receiving chemotherapy-surgery vs. other treatments (surgery only and surgery-chemotherapy) was adjusted for all significant variables on unadjusted analysis: year of diagnosis, age, great circle distance, hospital volume, gender, race, comorbidity, income, insurance, primary site of the cancer, facility type, staging, education, and surgical procedure of primary site.

Median survival in months was calculated using Kaplan-Meier estimates by determining the time from diagnosis after which 50% of patients with gastric cancer were still surviving.

Associations were deemed statistically significant at $p < 0.05$. Statistical analyses were performed using SAS version 9.4 and STATA SE version 15.0.

Results

Patient Characteristics

Of 15,947 included patients with pathological stage II or III primary gastric cancer, 15.7% of patients received chemotherapy-surgery while 84.3% of patients received surgery only or surgery-chemotherapy (Table 1). Patients who received chemotherapy-surgery tended to be younger, have a lower Charlson comorbidity index, and have higher income and educational status. Additionally, patients who received chemotherapy-surgery were more likely to be treated at academic healthcare centers or higher volume hospitals. Patients who received either surgery alone or surgery-chemotherapy were more likely to have tumors at the pylorus or gastric antrum and receive a partial gastrectomy.

Temporal Trends in Treatment Type

Before 2006, fewer than 5% of patients received chemotherapy-surgery (Fig. 1). After 2006, the proportion of patients receiving chemotherapy-surgery steadily increased. By 2015, 27.5% of patients received chemotherapy-surgery, while 72.5% of patients received other treatment strategies.

Predictors of Underutilization of Neoadjuvant Chemotherapy

On multivariable analysis with receipt of chemotherapy-surgery as the outcome of interest, factors associated with lack of neoadjuvant therapy included older patient age (OR 0.14, 95% CI 0.11–0.18) and higher Charlson comorbidity index (OR 0.61, 95% CI 0.49–0.76) (Fig. 2; Appendix). Treatment at higher volume hospitals (OR 1.31, 95% CI 1.10–1.56), academic research programs (OR 2.16, 95% CI 1.69–2.76) or integrated network cancer programs (OR 1.61, 95% CI 1.23–2.09), as well as undergoing total/subtotal (OR 2.28, CI 2.02-2.57) or en bloc gastrectomy (OR 1.73, 95% CI 1.50–2.01) predicted receipt of chemotherapy-surgery.

Median Survival

Overall, patients who received chemotherapy-surgery were associated with longer median survival than those who did not (30.62 months, 95% CI 28.98–32.79 vs. 26.61 months, 95% CI 25.72–27.63) (Table 2). Patients aged 80 or older who received chemotherapy-surgery had greater median length of survival than similarly aged patients who received other treatment strategies (50% survival 23.79 months, 95% CI 18.37–26.97 vs. 15.31 months, 95% CI 14.26–27.63).

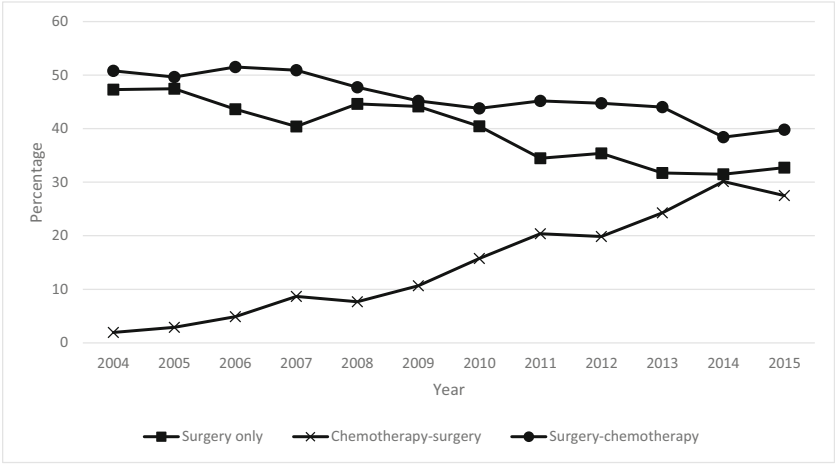

Fig. 1 Treatment type by year of pathological stage II/III gastric cancer patients

Discussion

Our findings suggest that more than a decade after the publication of the landmark MAGIC trial, fewer than 30% of patients in the USA with stage II and III primary gastric cancer are receiving neoadjuvant chemotherapy and surgery. Increased age was associated with lack of neoadjuvant therapy, despite greater median survival in older patients who received neoadjuvant chemotherapy. Predictors of receipt of neoadjuvant chemotherapy included treatment at academic research programs or high-volume hospitals and receipt of total/subtotal gastrectomy.

Using NCDB data, we found that from 2004 to 2015, the proportion of patients receiving neoadjuvant chemotherapy increased from less than 2 to 27.5%. However, by 2015, over 70% of patients still received treatments other than neoadjuvant chemotherapy and surgery. A similar trend was demonstrated in a retrospective cohort study by Greenleaf utilizing NCDB data of adult patients who underwent definitive gastrectomy for gastric cancer. They showed that for patients who underwent gastrectomy, there was a significant increase in the use of neoadjuvant chemotherapy from 2003 and 2012.[17] This increasing trend in the use of neoadjuvant chemotherapy has also been demonstrated by a retrospective cohort study by Snyder using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database.[11] Although these increasing trends are promising, it still remains highly concerning that in 2015, less than 1/3 of patients are receiving neoadjuvant chemotherapy. However, as discussed in a review by Morris, there is an average of 17 years of lag time between

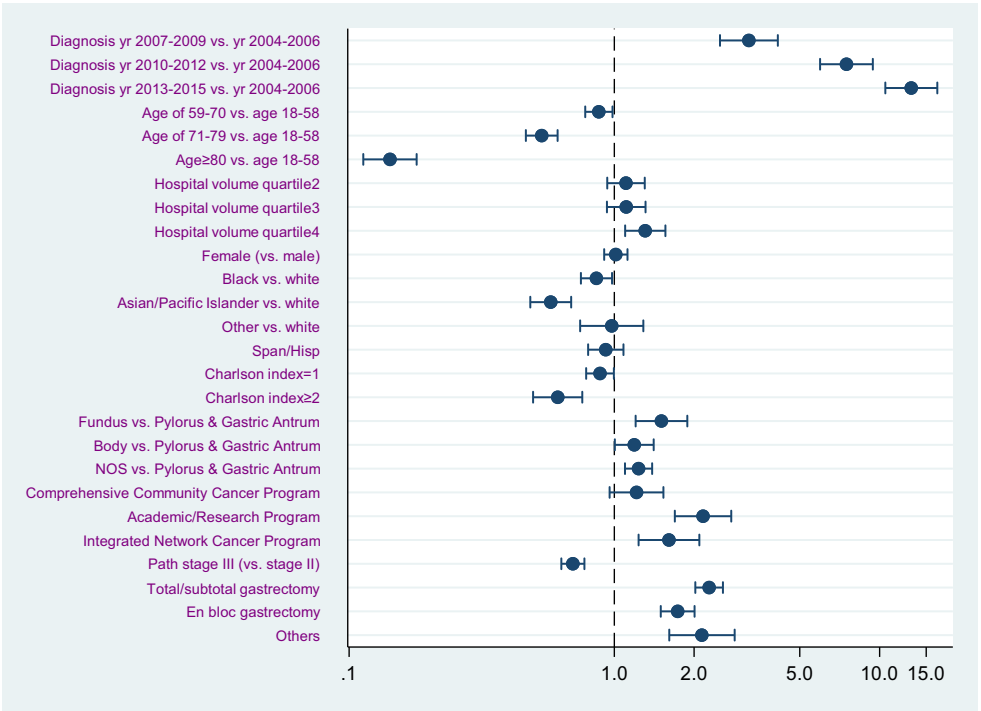

Fig. 2 Multivariable logistic regression model for receipt of perioperative chemotherapy and surgery vs. other treatments (surgery and surgery followed by chemotherapy) for pathological stage II/III gastric cancer patients. Covariates are shown on the *y*-axis. The *x*-axis represents odd ratios

Table 2 Median survival by age for patients receiving perioperative chemotherapy and surgery vs. other treatments (surgery and surgery followed by chemotherapy) for pathological stage II/III gastric cancer patients

Age categories	Surgery only or surgery-chemotherapy (N = 12,422)		Chemotherapy-surgery (N = 2111)	
	N	50% survival (95% CI) (months)	N	50% survival (95% CI) (months)
18–58	3372	40.31 (37.52, 43.99)	868	35.15 (30.62, 39.79)
59–70	3402	30.16 (28.09, 32.49)	752	31.15 (27.33, 35.02)
71–79	3141	23.46 (21.91, 25.23)	412	27.73 (23.46, 30.32)
80+	2507	15.31 (14.26, 16.36)	79	23.79 (18.37, 26.97)
Total	12,422	26.61 (25.72, 27.63)	2111	30.62 (28.98, 32.79)

publication of landmark evidence and implementation into clinical practice.[18]

We also found that patients older than the age of 80 were significantly less likely to receive neoadjuvant chemotherapy and surgery. Our group showed similar results using the SEER-Medicare database, demonstrating that elderly patients were significantly less likely to receive appropriate treatment for gastric cancer.[13] This is not a surprising finding, as the prevalence of frailty increases with age and results in decreased physiological reserve and functional status.[19] As a result, older patients are often viewed to be poor candidates for intensive treatment modalities, such as chemotherapy and surgery. Nevertheless, the literature is mixed on the impact of age and outcomes after multimodal treatment strategies for gastric cancer. In a systematic review and meta-analysis by Shen, older patients with greater frailty had a higher rate of adverse outcomes after receiving gastrectomy for gastric cancer.[20] However, our study demonstrated that appropriately selected older patients (80 years of age or older) had significantly greater median length of survival if they received neoadjuvant chemotherapy, compared with those who did not receive appropriate therapies. Similarly, a prospective study by Charalampakis demonstrated that older patients who received neoadjuvant treatment for gastroesophageal adenocarcinoma had similar rates of complications, mortality, and disease-free survival than their younger counterparts.[21] Other studies have shown that older patients who undergo major abdominal surgery, such as esophagectomy and pancreatectomy, have comparable outcomes with younger patients.[22, 23] Furthermore, retrospective studies by Tsushima and Aoyama demonstrated that the use of chemotherapy for the treatment of gastric cancer is both safe and feasible for older patients.[24, 25]

Patients who were treated at high volume hospitals or academic research programs were roughly 1.4 and 2 times more likely receive neoadjuvant chemotherapy and surgery. Similar to our findings, Sherman's retrospective cohort study of adults with gastric adenocarcinoma also showed that treatment at high-volume academic centers was a predictor of receiving neoadjuvant therapy.[12] Numerous studies have demonstrated improved outcomes with high-volume hospitals and surgeons for numerous medical and surgical conditions,[26] including general surgery[27] and upper gastrointestinal tract surgery.[28] Furthermore, a review of the literature by Ayanian found that academic institutions had improved outcomes as well as better overall quality of care compared with non-academic hospitals.[29] It is speculated that these differences in outcomes and quality of care may be related to the implementation of evidence-based practices. This is especially applicable in the treatment of locally advanced gastric cancer, as the use of neoadjuvant chemotherapy has only recently become the standard of care.

Our study also demonstrated that patients who underwent total/subtotal gastrectomy were more than 2 times more likely to have received neoadjuvant chemotherapy compared with those who underwent partial gastrectomy. Total/subtotal gastrectomy is a more complex procedure than a partial gastrectomy and often requires more complicated gastrointestinal reconstructions.[30–32] Due to their complexity, we suspect that patients who require total/subtotal gastrectomy are more likely to be referred to referral centers. As a result, these patients may ultimately receive care at tertiary referral centers or high-volume academic institutions. As previously discussed, receipt of care at a high-volume hospital or academic research program is a predictor of receiving neoadjuvant chemotherapy. Thus, the association between total/subtotal gastrectomy and neoadjuvant chemotherapy may be a reflection of referral patterns and where these subgroups of patients ultimately receive care and treatment.

Our study suggests that despite the benefits of neoadjuvant chemotherapy and surgery first demonstrated by the MAGIC trial and corroborated by numerous subsequent studies, fewer than 30% of patients with stage II and III gastric cancer are receiving neoadjuvant therapies. This is highly concerning, as neoadjuvant chemotherapy and surgery has been shown repeatedly to have improved progression-free survival. We identified numerous modifiable factors, such as patient age, surgical characteristics, and institution-related, that impact whether patients are likely to receive the standard of care treatment. Therefore, education of both providers and patients is indicated to ensure that all patients receive appropriate, evidence-based treatments for gastric cancer.

Our study has several limitations. There may be errors attributable to missing or inaccurately recorded data. Additionally, this is a retrospective observational study, so there may be unmeasured confounding that may bias our findings. Moreover, the NCDB data does not provide information on treatment intentions. By definition, patients who were included in our neoadjuvant chemotherapy and surgery group must have completed both chemotherapy and surgery to be included. There may be patients who intended to have neoadjuvant chemotherapy and surgery but only completed chemotherapy; these patients would not be included in the chemotherapy-surgery group. The NCDB data also does not specifically define neoadjuvant chemotherapy. We assumed all patients who underwent neoadjuvant chemotherapy would ultimately continue on to receive postoperative chemotherapy, to complete the standard of care perioperative chemotherapy regimen. Furthermore, we were unable to differentiate treatment strategies based on patient choice; NCDB data does not provide information on whether patients personally chose to forgo certain treatment modalities. Moreover, the NCDB does not provide specific data on chemotherapy regimens used and whether patients completed chemotherapy prior to receipt of surgery. However, this is similar to the results of the MAGIC trial, where not all patients completed chemotherapy prior to advancing to surgery.[7] Additionally, we were unable to perform further survival analyses due to how we defined our treatment groups. By definition, patients included in each group must have completed all treatment modalities, therefore excluding patients who did not survive. Thus, any models created for survival analyses would have had artificially high survival rates. Finally, our methodology used pathologic staging rather than clinical staging. While both staging methods may exclude some patients, we opted to use pathologic staging as it is a more reliable method of identifying lymph nodes compared with cross-sectional imaging alone.

Conclusions

More than ten years after the publication of the MAGIC trial, fewer than 1/3 of patients with stage II/III gastric cancer are receiving neoadjuvant chemotherapy and surgery, which has been shown to improve disease-specific survival. Further studies and interventions are needed to understand this underutilization and ensure both patients and providers are having evidence-based discussions about multimodal therapy for gastric cancer.

Contributorship All co-authors contributed to study design. YX, NL, and AOL contributed to data analysis. NL, YX, and AOL contributed to manuscript composition. All co-authors contributed in the data interpretation and manuscript revisions. All co-authors approved the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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Appendix. Univariate and multivariable logistic regression model for receipt of perioperative chemotherapy and surgery vs. other treatments for pathological stage II/III gastric cancer patients

Variable	Univariate		Multivariable	
	OR	*p* value	OR	95% CI
Year of diagnosis				
2004–2006	ref	-	ref	-
2007–2009	2.96	*< 0.001*	3.22	2.50–4.13
2010–2012	6.91	*< 0.001*	7.51	5.97–9.44
2013–2015	11.26	*< 0.001*	13.18	10.51–16.52
Age categories				
18–58	ref	-	ref	-
59–70	0.88	*0.013*	0.87	0.78–0.98

(continued)

Variable	Univariate		Multivariable	
	OR	*p* value	OR	95% CI
71–79	0.51	*< 0.001*	0.53	0.46–0.61
80+	0.13	*< 0.001*	0.14	0.11–0.18
Female (vs. male)	0.95	0.292	1.01	0.92–1.12
Race				
White	ref	-	ref	-
Black	0.91	0.087	0.86	0.75–0.98
Asian/Pacific Island	0.77	*< 0.001*	0.58	0.48–0.69
Other	1.33	*0.010*	0.98	0.74–1.29
Spanish or Hispanic	1.19	*0.003*	0.93	0.80–1.08
Comorbidity				
Score 0	ref	-	ref	-
Score 1	0.76	*< 0.001*	0.88	0.78–1.00
Score ≥ 2	0.48	*< 0.001*	0.61	0.49–0.76
Education 2008–2012 (not high school graduate)				
21% or more	ref	-	ref	-
13–20.9%	1.04	0.522	1.06	0.91–1.24
7–12.9%	1.17	*0.010*	1.32	1.11–1.57
Less than 7%	1.43	*< 0.001*	1.77	1.44–2.18
Income 2008–2012				
Less than $38,000	ref	-	ref	-
$38,000–$47,999	1.07	0.314	1.06	0.90–1.25
$48,000–$62,999	1.19	*0.007*	1.03	0.87–1.23
$63,000+	1.31	*< 0.001*	0.95	0.78–1.15
Insurance				
Not insured	ref	-	ref	-
Insured	0.86	0.116	1.03	0.82–1.28
Insurance status unknown	0.68	*0.034*	0.73	0.48–1.13
Primary site				
Pylorus and Gastric Antrum	ref	-	ref	-
Fundus	2.13	*< 0.001*	1.51	1.20–1.89
Body	1.61	*< 0.001*	1.19	1.00–1.41
NOS	1.41	*< 0.001*	1.23	1.10–1.39
Stage III (vs. stage II)	0.88	*0.002*	0.70	0.63–0.77
Surgical procedure of primary site				
Partial gastrectomy	ref	-	ref	-
Total/subtotal gastrectomy	2.70	*< 0.001*	2.28	2.02–2.57
En bloc gastrectomy	2.19	*< 0.001*	1.73	1.50–2.01
Others	2.11	*< 0.001*	2.14	1.61–2.84
Great Circle Distance (miles)	1.0012	*< 0.001*	1.0008	1.0004–1.0012
Hospital volume				
Quartile 1[1, 11] – mean 6.98	ref	-	ref	-
Quartile 2 [11, 22] – mean 16.51	1.34	*< 0.001*	1.11	0.94–1.30
Quartile 3 [22, 39] – mean 29.97	1.63	*< 0.001*	1.11	0.94–1.31
Quartile 4 [39, 273] – mean 74.81	2.26	*< 0.001*	1.31	1.10–1.56
Facility type				
Community Cancer Program	ref	-	ref	-
Comprehensive Community Cancer Program	1.45	*< 0.001*	1.21	0.96–1.53

(continued)

Variable	Univariate		Multivariable	
	OR	*p* value	OR	95% CI
Academic/Research Program	3.14	*< 0.001*	2.16	1.69–2.76
Integrated Network Cancer Program	2.11	*< 0.001*	1.61	1.23–2.09

References

1. Sitarz R, Skierucha M, Mielko J, Offerhaus JA, Maciejewski R, Polkowski WP. Gastric cancer: epidemiology, prevention, classification, and treatment. Cancer Manag Res 2018;10:239–48.
2. Ferlay J, Soerjomataram I, Dikshit R, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.
3. Macdonald JS. Gastric cancer - New therapeutic options. N Engl J Med 2006;355:76–7.
4. Ajani JA, D TA, Bentrem DJ, Chao J, Corvera C, Das P, Denlinger CS, Enzinger PC, Fanta P, Farjah F, Gerdes H, Glasgow RE, Hayman JA, Hochwald S, Hofstetter WL, Ilson DH, Jaroszewski D, Johung KL, Keswani RN, Kleinberg LR, Leong S, Ly QP, Matkowskyj KA, Mulcahy MF, Paluri RK, Park H, Perry KA, Pimiento J, Poultsides GA, Strong VE, Weksler B, Wiesner G, Willett CG, Wright CD. Gastric cancer. NCCN Guidel 2019:1–113
5. Jim MA, Pinheiro PS, Carreira H, Espey DK, Wiggins CL, Weir HK. Stomach cancer survival in the United States by race and stage (2001-2009): Findings from the CONCORD-2 study. Cancer 2017;123:4994–5013.
6. National Cancer Institute. SEER Stat fact sheets: stomach cancer. Available at: http://seer.cancer.gov/statfacts/html/stomach.html [Accessed: May 26, 2019].
7. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Howard Scarffe J, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Jo Chua Y, Wha S, Marsden Hospital R. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11–20.
8. Choi AH, Kim J, Chao J. Perioperative chemotherapy for resectable gastric cancer: MAGIC and beyond. World J Gastroenterol 2015;21:7343–8.
9. Al-Batran S-E, Homann N, Pauligk C, Illerhaus G, Martens UM, Stoehlmacher J, Schmalenberg H, Luley KB, Prasnikar N, Egger M, Probst S, Messmann H, Moehler M, Fischbach W, Hartmann JT, Mayer F, Höffkes H-G, Koenigsmann M, Arnold D, Kraus TW, Grimm K, Berkhoff S, Post S, Jäger E, Bechstein W, Ronellenfitsch U, Mönig S, Hofheinz RD. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: The AIO-FLOT3 trial. JAMA Oncol 2017;3:1237–44.
10. Al-Batran S-E, Homann N, Schmalenberg H, Kopp H-G, Haag GM, Luley KB, Schmiegel WH, Folprecht G, Probst S, Prasnikar N, Thuss-Patience PC, Fischbach W, Trojan J, Koenigsmann M, Pauligk C, Goetze TO, Jaeger E, Meiler J, Schuler MH, Hofheinz R. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A mul. J Clin Oncol 2017;35:4004–4004.
11. Snyder RA, Penson DF, Ni S, Koyama T, Merchant NB. Trends in the use of evidence-based therapy for resectable gastric cancer. J Surg Oncol 2014;110:285–90.
12. Sherman KL, Merkow RP, Bilimoria KY, Wang CE, Mulcahy MF, Benson AB, Bentrem DJ. Treatment trends and predictors of adjuvant and neoadjuvant therapy for gastric adenocarcinoma in the United States. Ann Surg Oncol 2013;20:362–70.
13. Liu N, Molena D, Stem M, Blackford AL, Sewell DB, Lidor AO. Underutilization of teratment for regional gastric cancer among the elderly in the USA. J Gastrointest Surg 2018;22:955–63.
14. American College of Surgeons: National Cancer Database. About the National Cancer Database. Available at: https://www.facs.org/quality-programs/cancer/ncdb/about [Accessed: May 26, 2019].
15. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: A powerful initiative to improve cancer care in the United States. Ann Surg Oncol 2008;15:683–90.
16. Washington K. 7th edition of the AJCC cancer staging manual: Stomach. Ann Surg Oncol 2010;17:3077–9.
17. Greenleaf EK, Hollenbeak CS, Wong J. Trends in the use and impact of neoadjuvant chemotherapy on perioperative outcomes for resected gastric cancer: Evidence from the American College of Surgeons National Cancer Database. Surgery 2016;159:1099–112.
18. Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: Understanding time lags in translational research. J R Soc Med 2011;104:510–20.
19. Chen X, Mao G, Leng SX. Frailty syndrome: An overview. Clin Interv Aging 2014;9:433–41.
20. Shen Y, Hao Q, Zhou J, Dong B. The impact of frailty and sarcopenia on postoperative outcomes in older patients undergoing gastrectomy surgery: a systematic review and meta-analysis. BMC Geriatr 2017;17:188–96.
21. Charalampakis N, Xiao L, Lin Q, Elimova E, Shimodaira Y, Harada K, Rogers JE, Mares J, Amlashi FG, Minsky BD, Das P, Hofstetter WL, Matamoros Jr A, Sagebiel TL, Blum-Murphy MA, Lee JH, Weston B, Bhutani MS, Mansfield PF, Estrella JS, Badgwell BD, Ajani JA. Co-morbidities rather than age impact outcomes in patients receiving preoperative therapy for gastroesophageal adenocarcinoma. Ann Surg Oncol 2017;24:2291–301.
22. Liu H-C, Chen Y-C, Chen C-H, Chen Y-J. Esophagectomy in elderly patients with esophageal cancer. Int J Gerontol 2010;4:176–9.
23. Turrini O, Paye F, Bachellier P, Sauvanet A, Cunha AS, Le Treut YP, Adham M, Mabrut JY, Chiche L, Delpero JR. Pancreatectomy for adenocarcinoma in elderly patients: Postoperative outcomes and long term results. Eur J Surg Oncol 2013;39:171–8.
24. Tsushima T, Hironaka S, Boku N, Machida N, Yamazaki K, Yasui H, Fukutomi A, Todaka A, Taniguchi H, Onozawa Y, Taku K. Comparison of safety and efficacy of S-1 monotherapy and S-1 plus cisplatin therapy in elderly patients with advanced gastric cancer. Int J Clin Oncol 2013;18:10–6.
25. Aoyama T, Yoshikawa T, Watanabe T, Hayashi T, Ogata T, Cho H, Tsuburaya A. Safety and feasibility of S-1 adjuvant chemotherapy for gastric cancer in elderly patients. Gastric Cancer 2012;15:76–82.
26. Amato L, Fusco D, Acampora A, Bontempi K, Rosa AC, Colais P, Cruciani F, D'Ovidio M, Mataloni F, Minozzi S, Mitrova Z, Pinnarelli L, Saulle R, Soldati S, Sorge C, Vecchi S, Ventura M, Davoli M. Volume and health outcomes: evidence from systematic

reviews and from evaluation of Italian hospital data. Epidemiol Prev 2017;41:1–128.
27. Mehta A, Efron DT, Canner JK, Dultz L, Xu T, Jones C, Haut ER, Higgins RS, Sakran J V. Effect of surgeon and hospital volume on emergency general surgery outcomes. J Am 2017;225:666–75.
28. Fischer C, Lingsma H, Klazinga N, Hardwick R, Cromwell D, Steyerberg E, Groene O. Volume-outcome revisited: The effect of hospital and surgeon volumes on multiple outcome measures in oesophago-gastric cancer surgery. PLoS One 2017;12:e0183955.
29. Ayanian JZ, Weissman JS. Teaching hospitals and quality of care: A review of the literature. Milbank Q 2002;80:569–93.
30. Syn NL, Wee I, Shabbir A, Kim G, So JB-Y. Pouch versus no pouch following total gastrectomy: Meta-analysis of randomized and non-randomized studies. Ann Surg 2019;269:1041–53.
31. Lehnert T, Buhl K. Techniques of reconstruction after total gastrectomy for cancer. Br J Surg 2004;91:528–39.
32. Hirao M, Takiguchi S, Imamura H, Yamamoto K, Kurokawa Y, Fujita J, Kobayashi K, Kimura Y, Mori M, Doki Y, Takiguchi S, Oncol AS. Comparison of Billroth I and Roux-en-Y reconstruction after distal gastrectomy for gastric cancer: One-year postoperative effects assessed by a multi-institutional RCT. Ann Surg Oncol 2013;20:1591–7.