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Lymph Node Evaluation after Neoadjuvant Chemotherapy for Patients with Gastric Cancer

Adrienne B. Shannon, MD[1], Richard J. Straker III, MD[1], Luke Keele, PhD[1], Douglas L. Fraker, MD[2], Robert E. Roses, MD[2], John T. Miura, MD[2], and Giorgos C. Karakousis, MD[2]

[1]Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA; [2]Division of Endocrine and Oncologic Surgery, Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA

ABSTRACT

Background. Adequate lymphadenectomy with at least 16 nodes retrieved at the time of gastrectomy is a quality measure recommended to ensure adequate staging. The minimum nodal retrieval recommended after receipt of neoadjuvant chemotherapy (NACT) is less defined.

Methods. Patients with clinical stages 1 to 3 gastric adenocarcinoma who received NACT and surgical resection were identified from the 2004–2015 National Cancer Database. The optimal nodal harvest number was calculated with Cox spline regression modeling. Cohorts with a nodal harvest higher or lower than this number were 1:1 propensity score-matched. Overall survival (OS) was analyzed using Kaplan-Meier survival estimates.

Results. Among 4337 patients receiving NACT, the optimal minimal nodal harvest at gastrectomy was 23 nodes. Compared with the patients who had fewer than 23 nodes retrieved, the patients with at least 23 nodes examined (n = 1073, 24.7%) were more likely to be female (26.1% vs 22%; p = 0.006) and non-white (29.3% vs 18.5%; $p <$ 0.0001), to have a Charlson-Deyo score of 0 (71.5% vs 66.8%; p = 0.005), and to have undergone resection at an academic facility (67.9% vs 51.5%; $p <$ 0.0001). The patients with at least 23 nodes examined had higher proportions of high-grade tumor (62% vs 57.4%; p = 0.030), pT3 or pT4 tumor (56.3% vs 48.7%; $p <$ 0.0001), body tumor (21.3% vs 12.5%; $p <$ 0.0001), or antrum/pylorus tumor (15.3% vs 11.4%; $p <$ 0.0001). The patients with at least 23 nodes were more likely to have lymph node metastases identified (61% vs 51%; $p <$ 0.0001). After matching, the patients with at least 23 nodes (n = 990) demonstrated an improved 5-year OS (57.9% vs 49%; p = 0.001).

Conclusions. The extent of lymphadenectomy during gastrectomy for gastric adenocarcinoma should not be reduced after NACT because adequate lymph node retrieval remains important for prognostication.

Gastric adenocarcinoma represents the fifth most common malignancy worldwide, with a significant age-adjusted mortality rate of 2.8 deaths per 100,000 persons.[1] Although its incidence has been declining in the United States (with an approximate decreased incidence of 1.4% between 2013 and 2017), gastric adenocarcinoma continues to have a poor prognosis, with an estimated average 5-year survival rate of 32%.[1]

Lymph node metastases is an important prognostic factor in gastric cancer, and adequate lymphadenectomy at the time of surgical resection is critical for staging and prognostication.[2–5] After the adoption of the American Joint Committee on Cancer (AJCC) eighth-edition staging criterion in 2017, the recommended lymph node retrieval number for adequate prognostication is 16 lymph nodes, with retrieval of fewer than 16 regional lymph nodes associated with an increase in inaccurate staging and worse survival.[6,7]

Although surgical resection remains the standard of care in localized, resectable disease for gastric cancer, perioperative chemoradiotherapy treatments have become mainstay methods in treatment.[3,8,9] Neoadjuvant chemotherapy for locally advanced gastric cancer is

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A. B. Shannon, MD
e-mail: Adrienne.shannon@pennmedicine.upenn.edu

associated with higher overall and progression-free survival, shorter postoperative hospital stay, and lower 30-day mortality rates.[2,5,8–15] The extent of lymphadenectomy after neoadjuvant therapy needed to optimize staging and prognostication has not been well-characterized, but some studies have associated a lower lymph node retrieval number after neoadjuvant chemotherapy (NACT) with inferior survival.[4,16,17]

Studies examining the optimal lymph node harvest number after neoadjuvant therapy in esophageal and rectal cancers have yielded somewhat conflicting results, with the number of recommended lymph nodes necessary for prognostication and improved survival being greater than the number recommended for esophageal cancer and less than the number recommended for rectal cancer.[18–21]

The extent of lymphadenectomy for gastrectomy after NACT to maintain optimal prognostication has not been clearly defined. Using a nationwide dataset, this study aimed to identify the minimum number of lymph nodes that should be retrieved at the time of gastric resection to optimize risk-stratification of survival outcomes for patients with gastric cancer who received NACT.

METHODS

Data Source and Patient Selection

This retrospective cohort study was performed using the 2004–2015 American College of Surgeons Commission on Cancer (CoC) National Cancer Database (NCDB) stomach Participant User File. This database is a validated instrument that has accrued data from more than 1500 CoC-affiliated facilities nationwide and contains clinical oncologic data including patient demographics, disease and treatment information, and survival outcomes.[22–24] The data included in the NCDB are de-identified from patient and facility and compliant with the Health Insurance Portability and Accountability Act. Given that this study involved retrospective review, it was deemed exempt from approval of our institutional review board.

Adult patients (age $\geq$18 years) who underwent first-line (i.e., neoadjuvant) chemotherapy with subsequent surgical resection for AJCC eighth-edition clinical stages 1 to 3 (i.e., non-metastatic) gastric adenocarcinoma were identified from the Participant User File. Gastric adenocarcinoma histology was defined by the International Classification of Diseases for Oncology, third edition (ICD-O-3) histology codes 8140 to 8147 and primary site code C16.x.

The study excluded 111 patients with an unknown number of lymph nodes examined at the time of surgical resection (Fig. 1) and 1705 patients who underwent local excision only (i.e., endoscopic resection). Also excluded were patients undergoing resection of contiguous structures in addition to gastrectomy (n = 813) or gastrectomy not otherwise specified (NOS) (n = 121) given the potentially significant heterogeneity (and subsequent associated morbidity and mortality) of these patient groups whose procedure details were limited. Surgical procedure type was classified by the Surveillance, Epidemiology, and End Results (SEER) surgery codes included in the NCDB.

The study also excluded 1308 patients with unknown tumor size, 435 patients with unknown grade of disease, 247 patients with unknown location of the tumor in the stomach, 197 patients with unknown or positive macroscopic surgical margins as defined by the NCDB criteria, and 34 patients with unknown receipt of radiotherapy. Patients who underwent definitive surgical resection fewer than 7 days after diagnosis and more than 360 days after diagnosis were excluded from the study (433 patients). The former patients were excluded because they were presumed to be resected on an urgent or emergent basis.

Variable Definitions

The primary end point of the study was 5-year overall survival (OS). The patient characteristics used in this study were age, sex, race/ethnicity (white, black, Asian, Hispanic, and unknown), education relative to the median (percentage of high school degrees within their zip code), income level relative to the median, insurance status, and Charlson-Deyo score. The facility characteristics included were geographic location, distance of residence from treatment facility, and hospital type. The tumor characteristics included were site of the tumor in the stomach (cardia or fundus, body or lesser/greater curvature, antrum or pylorus, or overlapping site of disease, as defined by the histologic codes in the NCDB), histologic subtype (adenocarcinoma NOS, linitis plastica, intestinal subtype, or diffuse type), tumor size, AJCC pT staging group, AJCC pN staging group, grade of disease, and presence of lymphovascular invasion.

The treatment characteristics included were type of surgical procedure, positive microscopic margins, number of total regional nodes examined, receipt of adjuvant chemotherapy (ACT), receipt of neoadjuvant radiotherapy (NART), and receipt of adjuvant radiotherapy (ART). The type of surgical procedure was determined using the following SEER Program Coding and Staging Manual 2018 surgery codes: partial gastrectomy NOS (30), antrectomy or distal gastrectomy (31 and 32), proximal gastrectomy (33), total gastrectomy (40 to 42), and total gastrectomy with partial esophagectomy (50 to 52).

The patients who met the inclusion criteria for the study were divided into two cohorts: those with fewer than the calculated optimal number of lymph nodes and those with

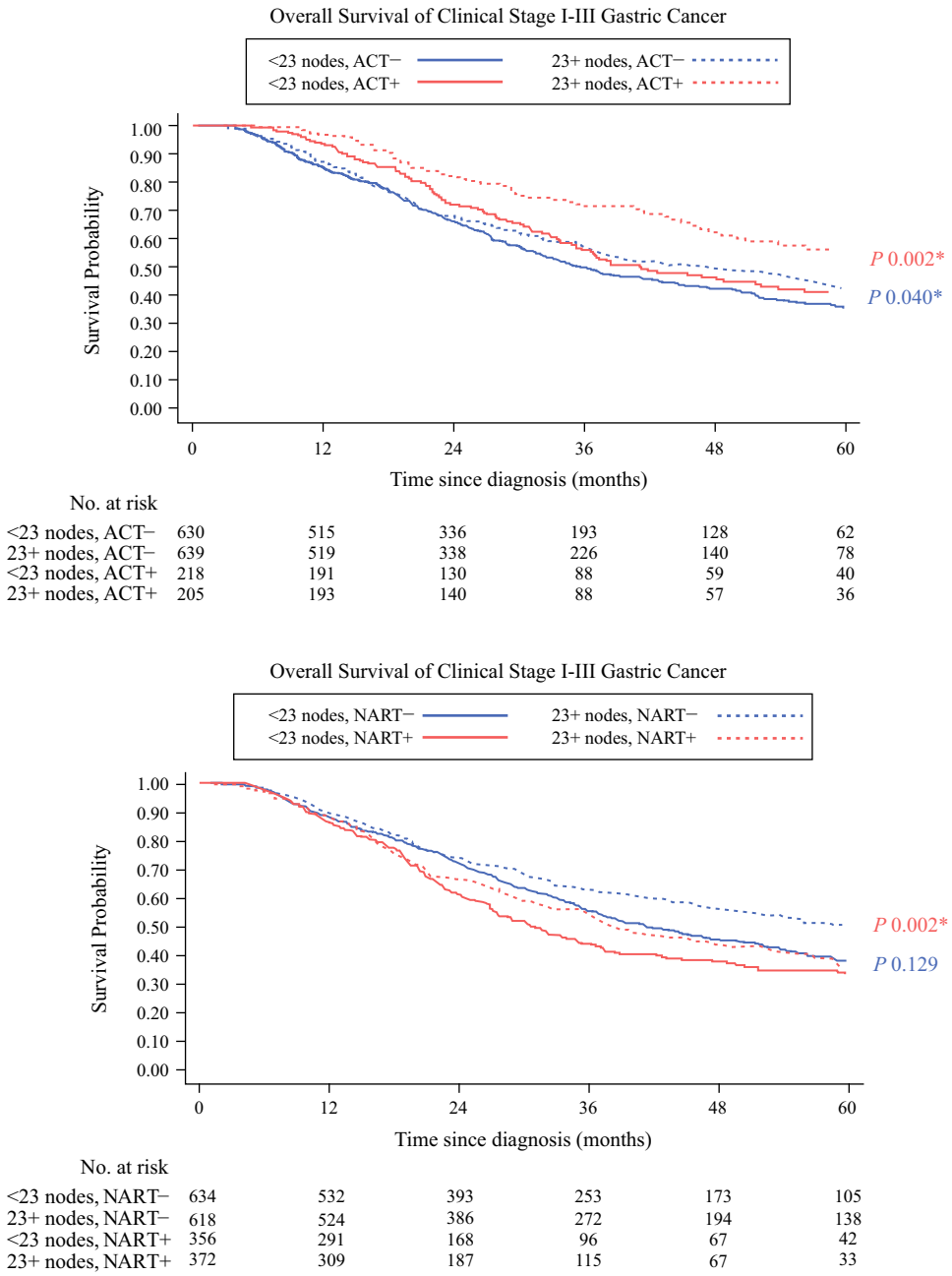

FIG. 1 Patients undergoing surgical resection and lymphadenectomy after neoadjuvant chemotherapy (NACT) for clinical stages 1 to 3 gastric adenocarcinoma. The study population was further subdivided into two cohorts based on spline regression modeling as follows: those with and those without 23 regional lymph nodes retrieved at the time of resection.

the optimal number of lymph nodes or more retrieved at the time of surgical resection, as determined by spline regression analysis. The lymph node ratio (LNR) was defined as the ratio of metastatic regional lymph nodes to the total number of retrieved lymph nodes.

Statistical Analysis

The optimal number of lymph nodes to be retrieved at the time of surgical resection was calculated based on Cox proportional hazards spline regression analysis. Spline regressions allow for investigation of the non-linear effects of continuous covariates, such as the number of retrieved lymph nodes.[25] An adjusted Cox proportional hazards spline regression of a 33% training dataset was used to determine a cutoff point (i.e., minimum number of lymph nodes) that optimized the 5-year OS for patients in the study population, which was validated with a 66% validation dataset (Fig. S1) using the survival, foreign, and splines packages for R 3.3.2 statistical software (R Foundation for Statistical Computing, Vienna, Austria).[26]

After determination of the optimal number of lymph node retrieved, the cohorts of patients who had fewer than this number were compared with those who had this

calculated number or more. Cohort differences were analyzed using univariate analyses with Pearson's chi-square and Wilcoxon's rank-sum test, as appropriate. Adjusted 5-year OS comparing the patients in these two cohorts was performed using Cox proportional hazards regression analysis with adjustment based on covariates significant for OS.

The patients from the two cohorts were propensity score-matched using a 1:1 propensity score-matching algorithm with a caliper distance of 0.10 of the standard deviation of the logit of the propensity score. All control subjects were used only once during the matching.

Adjusted Kaplan-Meier survival estimates with comparison by stratified log-rank test were used for further investigation of 5-year OS among the sub-populations. All missing or unknown variables were categorized as unknown in the univariate analyses and retained for further analyses. The 5-year OS start time was defined as the time of disease diagnosis by the referring facility, and the end time was defined as the time of death or last time of contact during a 5-year interval, with censoring as appropriate.

All the tests performed in this study were two-sided, with p values lower than 0.05 considered statistically significant. All statistical analyses were performed using Stata for Windows, version 13.1 (StataCorp LLC, College Station, TX) and R 3.3.2 statistical software.[26,27]

RESULTS

Patients with Gastric Adenocarcinoma Who Received Neoadjuvant Chemotherapy and Surgery

For the 4337 patients who received neoadjuvant chemotherapy and underwent surgical resection for clinical stages 1 to 3 gastric adenocarcinoma, the optimal minimal lymph nodal retrieval number was determined to be 23 nodes based on spline regression. The median age of all the patients was 64 years (interquartile range [IQR], 15 years), and 77% of the patients were male. For 1073 patients (24.7%), 23 or more regional lymph nodes were retrieved at the time of resection (Fig. 1).

Compared with the group that had fewer than 23 nodes retrieved, those with 23 or more nodes retrieved had a higher proportion females (26.1% vs 22%; $p = 0.01$), blacks (12.4% vs 8.7%;, $p < 0.0001$), Asians (7.4% vs 3.7%; $p < 0.0001$), and Charlson-Deyo scores of 0 (71.5% vs 66.8%; $p = 0.01$) (Table 1). The patients managed at academic centers (67.9% vs 51.5%, $p < 0.0001$) were more likely to have had 23 or more nodes retrieved at the time of surgical resection.

The tumor factors more common among the patients with 23 or more nodes retrieved than among those with fewer than 23 nodes retrieved were tumor within the body (21.3% vs 12.5%; $p < 0.0001$) or antrum/pylorus (15.3% vs 11.4%; $p < 0.0001$), intestinal (15.5% vs 8.9%; $p < 0.0001$) or diffuse (7.2% vs 3.2%, $p<0.0001$) histologic subtype, tumor size of 4 cm or larger (57.9% vs 48.7%; $p < 0.0001$), and poorly or undifferentiated grade of disease (62% vs 57.4%; $p = 0.030$). Compared with the patients who had fewer than 23 nodes retrieved, those who had 23 or more nodes retrieved presented with more advanced disease across pT staging group (pT3: 47.9% vs 44.6%; pT4: 8.4% vs 4.1%; $p < 0.0001$), pN staging group (pN2:17% vs 14.6%; pN3: 16.9% vs 5%; $p < 0.0001$), and pathologic staging group (stage 3: 43.7% vs 36.3%; stage 4: 3.3% vs 1.3%; $p < 0.0001$). Lymph node metastases were more common among the patients with 23 or more nodes retrieved than among those with fewer than 23 nodes retrieved (61% vs 50.9%; $p < 0.0001$).

In terms of treatment characteristics, the patients with 23 or more nodes retrieved were more likely to have undergone total gastrectomy (20.3% vs 10.4%; $p < 0.0001$), but less likely to have undergone total gastrectomy with partial esophagectomy than the patients with fewer 23 nodes retrieved. The patients with 23 or more nodes retrieved were more likely to have received ACT (22% vs 13.8%; $p < 0.0001$) than those with fewer than 23 nodes retrieved. However, NART was less frequently administered to the patients with 23 or more nodes retrieved than to those with fewer than 23 nodes retrieved (34.8% vs 55.4%; $p < 0.0001$). The median LNR was 0.1 (IQR, 0–0.36) for the patients with fewer than 23 nodes retrieved and 0.04 (IQR, 0–0.14) for those with 23 ore more nodes retrieved during lymphadenectomy ($p < 0.0001$).

Overall Survival of Patients with Gastric Cancer Stratified by the Number of Lymph Nodes Retrieved

Compared with retrieval of 23 or more nodes at the time of gastrectomy, fewer than 23 nodes retrieved was associated with worse 5-year OS (47.7% vs 56.9%; hazard ratio [HR], 1.26; $p < 0.0001$; Table 2). After adjustment for covariates, which were significantly associated with overall survival, 5-year OS remained significantly worse (HR, 1.27; $p < 0.0001$) for the patients with fewer than 23 nodes retrieved than for those with 23 or more nodes retrieved. The LNR was additionally associated with worse 5-year OS (HR, 2.91; $p < 0.0001$).

After 1:1 propensity score-matching, the patients who had 23 or more nodes retrieved ($n = 990$) and patients who had fewer than 23 nodes retrieved were balanced groups without significant covariate differences (Table S1). After matching, the patients with 23 or more nodes retrieved had a better 5-year OS (57.9% vs 49%; $p = 0.001$) than those with fewer than 23 nodes retrieved. In the subgroup of

TABLE 1 Baseline patient, facility, tumor, and treatment characteristics of patients with stages 1 to 3 gastric adenocarcinoma who received neoadjuvant chemotherapy and underwent surgical resection with <23 and ≥23 regional lymph nodes retrieved during resection

	<23 Nodes *n* (%)	≥23 Nodes *n* (%)	*p* Value
	3264 (75.3)	1073 (24.7)	
Median age: years (IQR)	64 (15)	64 (16)	1.000
Sex			0.006[a]
Male	2546 (78.0)	793 (73.9)	
Female	718 (22.0)	280 (26.1)	
Race/ethnicity			<0.0001[a]
White	2610 (80.0)	734 (68.4)	
Black	285 (8.7)	133 (12.4)	
Asian	119 (3.7)	79 (7.4)	
Hispanic	199 (6.1)	102 (9.5)	
Unknown	51 (1.6)	25 (2.3)	
Education			0.148
Above median	1720 (52.7)	602 (56.1)	
Below median	1495 (45.8)	455 (42.4)	
Unknown	49 (1.5)	16 (1.5)	
Income			0.327
Above median	1985 (60.8)	680 (63.4)	
Below median	1228 (37.6)	377 (35.1)	
Unknown	51 (1.6)	16 (1.5)	
Insurance status			0.256
No insurance	82 (2.5)	29 (2.7)	
Private	1473 (45.1)	489 (45.6)	
Medicare	1440 (44.1)	447 (41.7)	
Medicaid	196 (6.0)	81 (7.6)	
Government	41 (1.3)	11 (1.0)	
Unknown	32 (1.0)	16 (1.5)	
Charlson-Deyo score			0.005[a]
0	2181 (66.8)	767 (71.5)	
1	827 (25.3)	247 (23.0)	
≥2	256 (7.8)	59 (5.5)	
Geographic location			<0.0001[a]
Northeast	228 (7.0)	76 (7.1)	
Mid-Atlantic	539 (16.5)	308 (28.7)	
Southeast	660 (20.2)	163 (15.2)	
Midwest	1314 (40.3)	325 (30.3)	
West	457 (14.0)	173 (16.1)	
Unknown	66 (2.0)	28 (2.6)	
Hospital type			<0.0001[a]
Academic	1681 (51.5)	729 (67.9)	
Non-academic	1517 (46.5)	316 (29.5)	
Unknown	66 (2.0)	28 (2.6)	
Median miles from facility (IQR)	14.3 (32.6)	14.9 (39.4)	0.521
Site of tumor			<0.0001[a]
Cardia or fundus	2365 (72.5)	620 (57.8)	
Body of stomach	409 (12.5)	229 (21.3)	
Antrum or pylorus	372 (11.4)	164 (15.3)	
Overlapping sites	118 (3.6)	60 (5.6)	

Table 1 (continued)

	<23 Nodes *n* (%)	≥23 Nodes *n* (%)	*p* Value
	3264 (75.3)	1073 (24.7)	
Histology			<0.0001[a]
Adenocarcinoma NOS	2858 (87.6)	827 (77.1)	
Linitis plastica	10 (0.3)	3 (0.3)	
Intestinal subtype	291 (8.9)	166 (15.5)	
Diffuse subtype	105 (3.2)	77 (7.2)	
Tumor size (cm)			<0.0001[a]
<4	1676 (51.4)	452 (42.1)	
≥4	1588 (48.7)	621 (57.9)	
AJCC pT staging group			<0.0001[a]
pT1	802 (24.6)	202 (18.8)	
pT2	875 (26.8)	267 (24.9)	
pT3	1454 (44.6)	514 (47.9)	
pT4	133 (4.1)	90 (8.4)	
AJCC pN staging group			<0.0001[a]
pN0	1602 (49.1)	425 (39.6)	
pN1	1023 (31.3)	285 (26.6)	
pN2	477 (14.6)	182 (17.0)	
pN3	162 (5.0)	181 (16.9)	
Pathologic AJCC stage			<0.0001[a]
1	889 (27.2)	198 (18.5)	
2	1147 (35.1)	371 (34.6)	
3	1186 (36.3)	469 (43.7)	
4	42 (1.3)	35 (3.3)	
Grade of disease			0.030[a]
Well-differentiated	140 (4.3)	39 (3.6)	
Moderately differentiated	1250 (38.3)	369 (34.4)	
Poorly or undifferentiated	1874 (57.4)	665 (62.0)	
Lymphovascular invasion			<0.0001[a]
Present	566 (17.3)	274 (25.5)	
Absent	1282 (39.3)	417 (38.9)	
Unknown	1416 (43.4)	382 (35.6)	
Surgical procedure			<0.0001[a]
Partial gastrectomy NOS	450 (13.8)	136 (12.7)	
Antrectomy or distal gastrectomy	415 (12.7)	159 (14.8)	
Proximal gastrectomy	244 (7.5)	62 (5.8)	
Total gastrectomy	338 (10.4)	218 (20.3)	
Total gastrectomy with PE	1817 (55.7)	498 (46.4)	
Surgical microscopic margins			0.326
Positive	200 (6.1)	57 (5.3)	
Negative	3064 (93.9)	1016 (94.7)	
Median no. of regional lymph nodes retrieved (IQR)	12 (9)	29 (11)	<0.0001[a]
Receipt of ACT	450 (13.8)	236 (22.0)	<0.0001[a]
Receipt of NART	1807 (55.4)	373 (34.8)	<0.0001[a]
Receipt of ART	438 (13.4)	156 (14.5)	0.355

IQR, interquartile range; NOS, not otherwise specified; AJCC, American Joint Committee on Cancer; PE, partial esophagectomy; ACT, adjuvant chemotherapy; NART, neoadjuvant radiotherapy; ART, adjuvant radiotherapy

[a]Indicates significance

patients who received ACT (n = 686), the 5-year OS was 69.3% for the patients with 23 or more nodes retrieved versus 54.1% for the patients with fewer than 23 nodes retrieved (p = 0.002; Fig. 2). For the patients who did not receive ACT, the 5-year OS also differed significantly between those with 23 or more nodes retrieved and those with fewer than 23 nodes retrieved, but this difference was smaller (57.3% vs 50.2%; p = 0.04).

Survival for Gastric Cancer Patients Receiving Neoadjuvant Chemotherapy and Neoadjuvant Radiation Stratified by the Number of Lymph Nodes Retrieved

In a subgroup of patients who received NART (n = 2180) within the larger study population, those with and without 23 or more nodes retrieved did not differ significantly in 5-year OS (54.3% vs 47.2%; p = 0.13). Conversely, among the patients who did not receive NART in addition to their NACT, those who had 23 or more nodes retrieved had a better 5-year OS (60% vs 50%; p = 0.002) than those with fewer than 23 nodes retrieved.

Additionally, the patients who did (n = 568) and those who did not receive NART in addition to their NACT before surgical resection were 1:1 propensity score-matched, with appropriate balance of covariates (Table S2). Among the patients who had 23 or more nodes retrieved, those who received NART did not differ significantly in 5-year OS from those who did not (51.4% vs 48.6%; p = 0.14). In contrast, among the patients who had fewer than 23 nodes retrieved, the patients who received NART had a worse 5-year OS (44.4% vs 55.6%; p = 0.04).

DISCUSSION

Despite a declining incidence in the United States, gastric adenocarcinoma remains a significant cause of gastrointestinal cancer-related deaths (2.8 deaths per 100,000 persons).[1] Lymph node metastases are among the most important prognostic factors in this disease, which has resulted in significant investigation regarding the adequacy of lymphadenectomy at the time of surgical resection.[2–5] Currently, 16 regional lymph nodes are the minimum recommended number of lymph nodes to be retrieved for optimal staging and disease-specific survival. However, with increased adoption of neoadjuvant therapies, particularly chemotherapy, for this patient population, some studies have suggested that this number may be inadequately risk-stratifying patients who have received neoadjuvant chemotherapy with a pathologic response.[6,7] This study aimed to determine the extent of lymphadenectomy that optimizes survival for patients with gastric cancer who receive neoadjuvant chemotherapy and surgical resection.

The study identified 23 as the optimal minimum number of regional lymph nodes retrieved for predicting survival among patients with clinical stages 1 to 3 gastric cancer who received neoadjuvant chemotherapy before surgical resection. This finding is consistent with a prior study of esophageal cancer recommending a greater number of retrieved lymph nodes after neoadjuvant therapy.[21] Receipt of perioperative chemotherapy has become a more prominent component of gastric cancer management with increased adoption of multimodality treatments to improve progression-free survival.[5, 8–15] However, despite this increased adoption of multimodality treatments, few studies have investigated how, if at all, this should influence the extent of surgery and lymphadenectomy.

A recent institutional study by Erstad et al. investigated a patient population in which 65% had received preoperative therapy. Their study demonstrated that retrieval of 30 or more regional lymph nodes at the time of gastric resection was associated with improved overall survival. Additionally, the prior FLOT-4 randomized controlled trial analyzing locally resectable gastric cancer patients had a median lymph node retrieval number of 25.31 Taken together with these investigations, growing evidence supports the role of more regional lymph nodes retrieved at the time of surgical resection of gastric cancer from patients receiving preoperative therapy.

In the current study, the patients who had 23 or more regional lymph nodes retrieved at the time of resection tended to have fewer comorbidities, suggesting a potential selection bias influencing the extensiveness of resection. Larger, high-grade, diffuse subtype, and higher N stage tumors all were associated with receipt of a more extensive lymphadenectomy, which also reflects potential tumor factors that may influence the decision for extensiveness of surgery. Descriptive findings of those who retrieved fewer than 23 as well as 23 or more regional lymph nodes appear most reflective of the location and biology of the tumor, suggesting that the nodal harvest is likely reflective of the regional basins associated with the surgical procedure type (i.e., proximal, distal, or total gastrectomy) as well as how the provider perceives the pathologic features of the tumor.

In addition to improving staging, increased lymph node retrieval could direct further therapies. Patients with 23 or more regional lymph nodes retrieved were more likely to be identified with nodal metastases, but also were more likely to undergo adjuvant therapy than those with fewer than 23 nodes retrieved. Although extensiveness of lymphadenectomy with respect to anatomic dissection has been associated with an increase in morbidity (i.e., D2 vs D1

TABLE 2 Rates of 5-year overall survival (OS) for patients with clinical stages 1 to 3 gastric cancer who received neoadjuvant chemotherapy and surgical resection based on uni- and multivariable Cox proportional hazards regression analyses

	Univariate analyses		Multivariable analyses	
	HR (CI)	*p* Value	HR (CI)	*p* Value
<23 Nodes vs ≥23 nodes	1.26 (1.14–1.40)	<0.0001[a]	1.27 (1.13–1.40)	<0.0001[a]
Age	1.01 (1.01–1.01)	<0.0001[a]	1.02 (1.01–1.02)	<0.0001[a]
Sex				
Male	1.07 (0.96–1.18)	0.205	Ref.	
Female	Ref.		1.01 (0.91–1.13)	0.791
Race/ethnicity				
White	1.57 (1.24–1.97)	<0.0001[a]	1.20 (0.94–1.53)	0.144
Black	1.16 (0.89–1.97)	0.271	1.01 (0.77–1.33)	0.937
Asian	Ref.		Ref.	
Hispanic	1.19 (0.90–1.59)	0.229	1.05 (0.78–1.40)	0.742
Unknown	0.99 (0.64–1.55)	0.981	0.92 (0.58–1.44)	0.709
Education				
Above median	Ref.		Ref.	
Below median	1.02 (0.94–1.11)	0.576	–	–
Unknown	0.70 (0.47–1.06)	0.097	–	–
Income				
Above median	Ref.		Ref.	
Below median	1.13 (1.04–1.23)	0.005 [a]	1.08 (0.98–1.18)	0.109
Unknown	0.73 (0.49–1.09)	0.129	0.68 (0.45–1.03)	0.066
Insurance status				
No insurance	1.36 (0.82–2.25)	0.241	–	–
Private	1.10 (0.71–1.72)	0.661	–	–
Medicare	1.40 (0.90–2.19)	0.133	–	–
Medicaid	1.08 (0.67–1.73)	0.752	–	–
Government	Ref.		–	–
Unknown	1.39 (0.78–2.50)	0.263	–	–
Charlson-Deyo score				
0	Ref.		Ref.	
1	1.14 (1.04–1.26)	0.007[a]	1.11 (1.00–1.22)	0.041[a]
≥2	1.27 (1.09–1.49)	0.003[a]	1.24 (1.06–1.46)	0.008[a]
Geographic location				
Northeast	1.04 (0.85–1.27)	0.704	1.04 (0.85–1.27)	0.697
Mid-Atlantic	Ref.		Ref.	
Southeast	1.47 (1.28–1.68)	<0.0001[a]	1.40 (1.21–1.61)	<0.0001[a]
Midwest	1.41 (1.25–1.60)	<0.0001[a]	1.32 (1.16–1.50)	<0.0001[a]
West	1.21 (1.04–1.41)	0.013 [a]	1.17 (1.00–1.36)	0.057
Unknown	1.35 (1.01–1.81)	0.042 [a]	2.06 (1.49–2.84)	<0.0001[a]
Hospital type				
Academic	Ref.		Ref.	
Non-academic	1.31 (1.20–1.42)	<0.0001[a]	1.15 (1.05–1.26)	0.002[a]
Unknown	1.20 (0.91–1.58)	0.208	–	–
Miles from facility	1.00 (1.00–1.00)	0.940	–	–
Site of tumor				
Cardia or fundus	1.43 (1.25–1.65)	<0.0001[a]	1.28 (1.06–1.54)	0.008[a]
Body of stomach	1.06 (0.89–1.27)	0.495	1.00 (0.84–1.20)	0.981
Antrum or pylorus	Ref.		Ref.	

Table 2 (continued)

	Univariate analyses		Multivariable analyses	
	HR (CI)	*p* Value	HR (CI)	*p* Value
Overlapping sites	1.44 (1.13–1.84)	0.003[a]	1.09 (0.85–1.40)	0.501
Histology				
Adenocarcinoma NOS	1.27 (1.10–1.47)	0.002[a]	1.01 (0.86–1.18)	0.924
Linitis plastica	3.07 (1.71–5.50)	<0.0001[a]	3.03 (1.67–5.49)	<0.0001[a]
Intestinal subtype	Ref.		Ref.	
Diffuse subtype	1.44 (1.13–1.84)	0.003 [a]	1.33 (1.03–1.72)	0.026[a]
Tumor size (cm)				
<4	Ref.		Ref.	
≥4	1.21 (1.11–1.32)	<0.0001[a]	1.06 (0.97–1.16)	0.209
AJCC pT staging group				
pT1	Ref.		Ref.	
pT2	1.32 (1.15–1.51)	<0.0001[a]	1.16 (1.00–1.35)	0.048[a]
pT3	2.00 (1.77–2.25)	<0.0001[a]	1.40 (1.20–1.63)	<0.0001[a]
pT4	2.60 (2.13–3.17)	<0.0001[a]	1.97 (1.54–2.51)	<0.0001[a]
AJCC pN staging group				
pN0	Ref.		Ref.	
pN1	1.73 (1.56–1.92)	<0.0001[a]	1.50 (1.31–1.72)	<0.0001[a]
pN2	2.36 (2.10–2.66)	<0.0001[a]	1.95 (1.62–2.33)	<0.0001[a]
pN3	3.00 (2.60–3.47)	<0.0001[a]	2.51 (2.03–3.09)	<0.0001[a]
Pathologic AJCC staging group				
1	Ref.		Ref.	
2	1.47 (1.29–1.67)	<0.0001[a]	1.09 (0.93–1.27)	0.302
3	2.59 (2.30–2.92)	<0.0001[a]	1.13 (0.91–1.40)	0.260
4	3.58 (2.72–4.71)	<0.0001[a]	1.25 (0.88–1.77)	0.208
Grade of disease				
Well-differentiated	Ref.		Ref.	
Moderately differentiated	1.60 (1.23–2.10)	0.001[a]	1.48 (1.13–1.94)	0.005[a]
Poorly or undifferentiated	2.02 (1.55–2.64)	<0.0001[a]	1.69 (1.30–2.22)	<0.0001[a]
Lymphovascular invasion				
Present	1.82 (1.62–2.04)	<0.0001[a]	1.27 (1.12–1.44)	<0.0001[a]
Absent	Ref.		Ref.	
Unknown	1.20 (1.08–1.32)	<0.0001[a]	1.06 (0.94–1.20)	0.318
Surgical procedure				
Partial gastrectomy NOS	1.08 (0.90–1.28)	0.413	1.05 (0.88–1.26)	0.564
Antrectomy or distal gastrectomy	Ref.		Ref.	
Proximal gastrectomy	1.35 (1.10–1.64)	0.003[a]	1.28 (1.03–1.59)	0.024[a]
Total gastrectomy	1.21 (1.02–1.44)	0.030[a]	1.19 (0.99–1.43)	0.070
Total gastrectomy with PE	1.44 (1.25–1.65)	<0.0001[a]	1.26 (1.06–1.48)	0.007[a]
Surgical microscopic margins	2.21 (1.91–2.56)	<0.0001[a]	1.52 (1.30–1.77)	<0.0001[a]
Receipt of ACT	0.80 (0.70–0.90)	<0.0001[a]	0.80 (0.70–0.92)	0.001[a]
Receipt of NART	1.20 (1.10–1.30)	<0.0001[a]	1.29 (1.14–1.45)	<0.0001[a]
Receipt of ART	1.02 (0.91–1.15)	0.755	–	–

HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; AJCC, American Joint Committee on Cancer; PE, partial esophagectomy; ACT, adjuvant chemotherapy; NART, neoadjuvant radiation; ART, adjuvant radiation

[a]Indicates significance

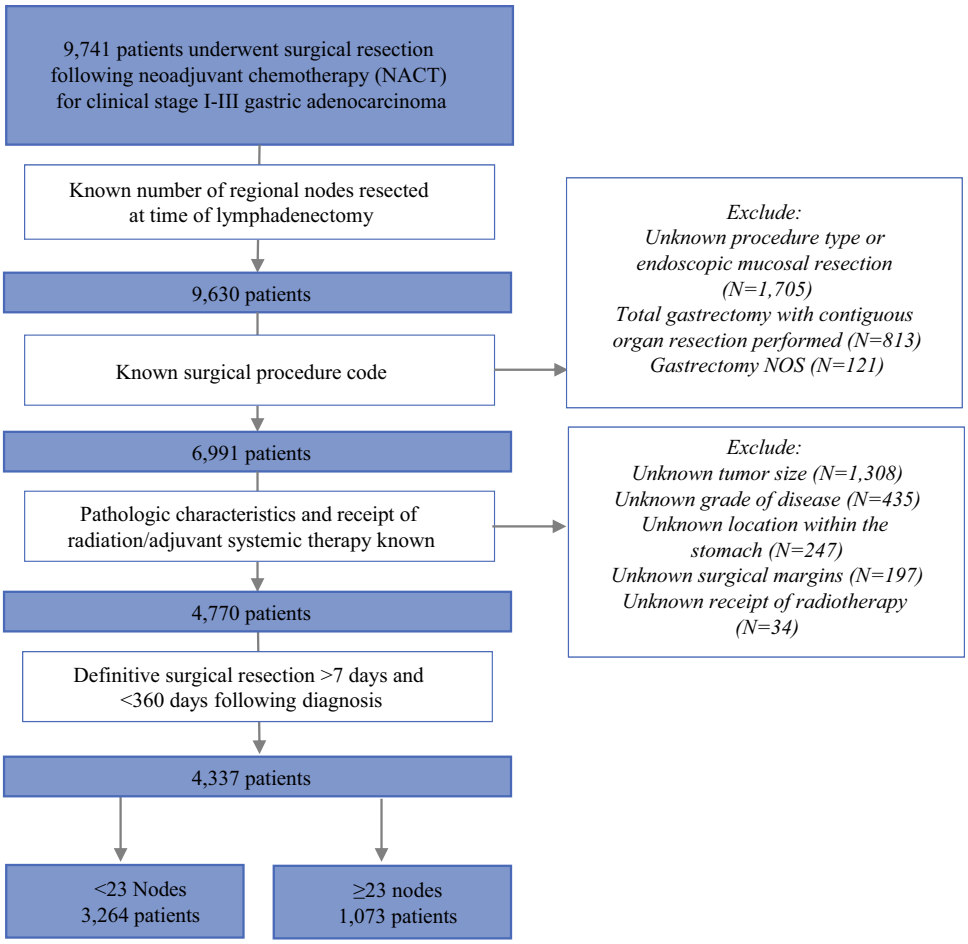

FIG. 2 Rates of 5-year overall survival (OS) for patients with gastric cancer who underwent neoadjuvant chemotherapy (NACT) and surgical resection with or without adjuvant chemotherapy (ACT) or neoadjuvant radiation (NART) and did or did not have 23 or more regional lymph nodes retrieved at the time of resection. *Indicates significance

lymphadenectomy), which could translate to a delay or lack of receipt of adjuvant therapies, it is notable that a greater number of lymph nodes retrieved was associated with an increase in receipt of adjuvant therapies. Additional study that more specifically investigates how the pathologic status of lymph nodes after neoadjuvant therapies influences the type and duration of subsequent adjuvant therapy is warranted to better define this relationship.

To date, prior literature has shown persistent nodal metastasis and minimal tumor regression after neoadjuvant therapy and surgical resection to be associated with worse overall survival.[28,29] A single-institution study examining whether alteration in the adjuvant therapy regimen (i.e., deviation from the proposed perioperative regimen) influenced overall survival for all gastric cancer patients found no impact on overall survival for patients with less than 50% histologic tumor regression whose regimen was altered.[30] However, patients with stage 3 disease after neoadjuvant treatments showed improved overall survival, suggesting that such patients with a poor primary tumor response and those with nodal metastases may be benefit from alterations in changing treatment from the neoadjuvant regimen.[30] Additionally, given the prognostic impact of lymph node metastases in gastric cancer, the implications of not identifying lymph node metastases in this population has a significant impact on patients' survival outcomes.[6,7] As such, our findings suggest that the number of nodes examined after NACT for gastric cancer may have particular import with regard to both prognostication and further treatment decisions. In particular, the lymph node ratio was found in this study, as in prior studies, to be associated with overall survival for this patient population and may help to inform decisions for adjuvant therapy.[31,32] Our study adds to the current literature in support of increased lymph node evaluation and analysis for prognostication and potential therapeutic guidance.[28–32] Addition of neoadjuvant radiotherapy to chemotherapy has been shown to increase the incidence of complete pathologic response after curative resection, although it does not appear to improve overall or recurrence-free survival. In the current study, patients' receipt of neoadjuvant

chemoradiotherapy was associated with a lower likelihood that 23 or more regional lymph nodes would be retrieved at the time of resection. Interestingly, although the patients with more than 23 lymph nodes retrieved had a survival advantage in the overall cohort, the patients who received neoadjuvant radiation in addition to neoadjuvant chemotherapy did not demonstrate a survival advantage with a higher lymph node yield. This suggests that a more extensive lymphadenectomy may not improve prognostication for patients undergoing local therapy to the nodal basin with radiation, potentially due to the lower likelihood that the pathologic status of the radiated node will be informative in determining the risk for distant metastases. Although our findings argue for an extended lymphadenectomy for patients who receive neoadjuvant chemotherapy and resection for gastric cancer, achieving this extended resection may have less utility for those who receive neoadjuvant chemoradiotherapy. Further studies evaluating an adequate lymphadenectomy for this particular population could help to address whether the optimal lymph node retrieval number is similar to or different from the general recommendations for patients undergoing surgical resection for gastric adenocarcinoma.

This study had several limitations due to its retrospective study design with potential inherent biases and unaccounted for confounding variables. This study examined the association of lymphadenectomy with overall survival, not disease-specific survival or progression-free survival (outcomes not available in the NCDB). Although the majority of deaths from this aggressive malignancy are presumably disease-related, deaths could be attributable to other causes. Additionally, pathologic response is not available in the NCDB, which can have an impact on patient prognosis. The extent to which an imbalance in this variable would exist between the two lymph node retrieval groups is not clear, even when matching is performed for other covariates.

This study also selected only for patients with known histologic and pathologic factors (i.e., tumor size, grade, and pathologic T staging group) to optimize our ability to interpret the association between these factors and oncologic outcomes. As such, selection bias may have occurred.

Finally, there may have been variability in the chemotherapy regimens used, as well as in the radiation therapy doses and methodology for the patients in this study, although it again is not clear to what extent these differences would vary between the two lymph node retrieval groups after matching. The ability to discern differences in these chemotherapy or radiation regimens is not available through the NCDB and could have an impact on patients' outcomes, particularly if some patients were unable to fully complete their prescribed treatment course before definitive surgical resection. Additionally, the influence of adjuvant therapies on overall survival is not without immortal time bias, particularly given the high morbidity associated with gastric resection for cancer, which may limit the patient's ability to proceed with or complete adjuvant therapies.[33] This limits interpretation of the impact that nodal retrieval has on patients receiving adjuvant chemotherapy regimens.

Despite these limitations, the current study highlights the prognostic importance of adequate lymph node retrieval at the time of gastrectomy after neoadjuvant chemotherapy for gastric cancer. The current study results do not support a reduction in the extensiveness of lymph nodal retrieval during surgical resection for this patient population after neoadjuvant chemotherapy. Rather, a more generous lymph node retrieval may more optimally prognosticate for patients after surgery, particularly in the absence of neoadjuvant radiation. Further prospective evaluation of this topic is warranted to validate these findings.

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