J Gastric Cancer. 2020 Sep;20(3):313-327
https://doi.org/10.5230/jgc.2020.20.e29
pISSN 2093-582X·eISSN 2093-5641

jgc Journal of Gastric Cancer

Original Article

Preoperative Therapy Regimen Influences the Incidence and Implication of Nodal Downstaging in Patients with Gastric Cancer

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Received: Apr 30, 2020
Revised: Jul 8, 2020
Accepted: Sep 1, 2020

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Presentation
This work has been accepted for presentation at the 2020 Society of Surgical Oncology International Conference on Surgical Cancer Care in Boston, MA on August 17-20, 2020.

Funding
Supported in part by the NIH/NCI under award number P30CA016672 and the Clinical Trials Support Resource.

Author Contributions
Conceptualization: S.A.P, I.N.; Data curation: S.A.P., I.N., C.Y.J.; Formal analysis: C.Y.J.; Investigation: S.A.P., I.N., C.Y.J.; Methodology: S.A.P., I.N., C.Y.J.; Project administration: I.N.; Resources: S.A.P., B.M.M., C.Y.J., D.P., M.B.D., E.J.S., A.J.A., B.B.D., M.P., I.N.; Software:

ABSTRACT

Purpose: Nodal downstaging after preoperative therapy for gastric cancer has been shown to impart excellent prognosis, but this has not been validated in a national cohort. The role of neoadjuvant chemoradiation (NACR) in nodal downstaging remains unclear when compared with that of neoadjuvant chemotherapy alone (NAC). Furthermore, it is unknown whether the prognostic implications of nodal downstaging differ by preoperative regimen.
Materials and Methods: Using the National Cancer Database, overall survival (OS) duration was compared among natural N0 (cN0/ypN0), downstaged N0 (cN+/ypN0), and node-positive (ypN+) gastric cancer patients treated with NACR or NAC. Factors associated with nodal downstaging were examined in a propensity score-matched cohort of cN+ patients, matched 1:1 by receipt of NACR or NAC.
Results: Of 7,426 patients (natural N0 [n=1,858, 25.4%], downstaged N0 [n=1,813, 24.4%], node-positive [n=3,755, 50.4%]), 58.2% received NACR, and 41.9% received NAC. The median OS durations of downstaged N0 (5.1 years) and natural N0 (5.6 years) patients were similar to one another and longer than that of node-positive patients (2.1 years) (P<0.001). In the matched cohort of cN+ patients, more recent diagnosis (2010–2015 vs. 2004–2009) (odds ratio [OR], 2.57; P<0.001) and NACR (OR, 2.02; P<0.001) were independently associated with nodal downstaging. The 5-year OS rate of downstaged N0 patients was significantly lower after NACR (46.4%) than after NAC (57.7%) (P=0.003).
Conclusions: Downstaged N0 patients have the same prognosis as natural N0 patients. Nodal downstaging occurred more frequently after NACR; however, the survival benefit of nodal downstaging after NACR may be less than that when such is achieved by NAC.

Keywords: Gastric cancer; Gastrectomy; Chemotherapy; Chemoradiation; Neoadjuvant therapy

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C.Y.J.; Supervision: I.N.; Visualization: S.A.P., I.N., C.Y.J.; Writing - original draft: S.A.P., I.N. ; Writing - review & editing: S.A.P., B.M.M., C.Y.J., D.P., M.B.D., E.J.S., A.J.A., B.B.D., M.P., I.N.

Conflict of Interest

Prajnan Das has received an honorarium from Adlai Nortye, Ltd.

INTRODUCTION

Multimodal therapy is currently the standard of care for patients with localized gastric cancer, and the use of preoperative therapy has increased in recent years [1,2]. Beginning with the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial, its use has been bolstered by data from randomized clinical trials demonstrating a survival benefit compared with surgery alone [3-5]. Although randomized data have shown a survival benefit for adjuvant radiation therapy, it remains unclear whether neoadjuvant chemoradiation (NACR) imparts a benefit over neoadjuvant chemotherapy alone (NAC) [6,7]. Forthcoming randomized trials (Trial Of Preoperative therapy for Gastric and Esophagogastric junction AdenocaRcinoma [TOPGEAR] and Randomized Phase III Trial of Adjuvant Chemotherapy or Chemoradiotherapy in Resectable Gastric Cancer [CRITICS]-II) aim to answer this question [8,9].

In alignment with the trend towards preoperative therapy, the American Joint Committee on Cancer's *AJCC Cancer Staging Manual* 8th edition introduced a new post-neoadjuvant therapy staging system (ypTNM) [10]. Previous analyses have shown that survival after preoperative therapy is more accurately predicted by ypTNM grouping than by cTNM grouping [11]. Patients with a pathological complete response (ypT0N0) experience prolonged survival, and this response may be more common after NACR than after NAC alone [11-16]. However, it has been commonly reported that overall survival (OS) does not significantly differ between these patients, despite NACR being more often associated with pathological complete response [16]. This begs the question whether the prognostic implications of pathological complete response (and ypTNM categories) differ on the basis of the type of preoperative therapy regimen used.

ypN status may be the most important predictor of outcome in gastric cancer patients who undergo preoperative therapy [17]. Persistent positive nodal disease (ypN+) can occur in patients who achieve ypT0, and in such cases, it markedly decreases survival [18]. Conversely, the ypT category does not influence survival among ypN0 patients [19]. Using institutional data, the present group recently reported that patients with downstaged N0 status (clinically node positive but post-treatment node negative [cN+/ypN0]) have the same OS as do patients with natural N0 status (cN0/ypN0) [20]. The excellent survival results observed in cN+/ypN0 patients indicated that nodal downstaging should be an important objective of preoperative therapy in patients with node-positive gastric cancer. However, this has not been examined in a multi-institutional cohort, and the factors associated with nodal downstaging are largely unknown. Specifically, the role of NACR in nodal downstaging is unclear, even though it is known to induce ypT0 more often than does NAC [16]. Moreover, it is unknown whether the prognostic implications of nodal downstaging differ by preoperative therapy regimen. Therefore, the present study was conducted to validate the prognostic significance of nodal downstaging in gastric cancer using the National Cancer Database (NCDB) and to elucidate the factors associated with nodal downstaging in a cohort of cN+ patients, with specific attention to the effects of NACR versus those of NAC.

MATERIALS AND METHODS

Data source

The NCDB was used for analysis, which draws clinical data from more than 1,500 Commission on Cancer-accredited cancer programs in the United States and Puerto Rico.

https://doi.org/10.5230/jgc.2020.20.e29

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A joint endeavor of the American College of Surgeons and the American Cancer Society, the NCDB began in 1989 and now contains approximately 34 million records. It is estimated that this system captures data on approximately 70% of newly diagnosed cancers in the United States [21].

Inclusion and exclusion criteria

All patients were identified who had been reported to the NCDB between 2004 and 2015 with invasive, non-metastatic (clinical stage cM0) gastric adenocarcinoma (histology codes 8140 [adenocarcinoma NOS], 8144 [intestinal-type adenocarcinoma], 8145 [diffuse-type adenocarcinoma], 8481 [mucinous adenocarcinoma], and 8490 [signet-ring cell adenocarcinoma]) who had received NACR or NAC followed by gastrectomy (surgical procedure code 30–80 [gastrectomy NOS, near-total or total gastrectomy, gastrectomy NOS with removal of a portion of the esophagus, and gastrectomy with resection in continuity with the resection of other organs]). Patients that had received NAC were defined as those that had received preoperative chemotherapy alone; NACR was defined as having received both preoperative chemotherapy and preoperative radiation therapy. Patients that had received preoperative radiation therapy were identified using surgery-radiation sequence code 2 (radiation given before surgery) or 4 (radiation given before and after surgery). Because a treatment sequence code was not available prior to 2006, patients who had received preoperative chemotherapy were identified by comparing the date of chemotherapy with the date of surgery. To improve the validity of the study, patients who had undergone chemotherapy <30 or >365 days prior to surgery were excluded. Patients with incomplete survival data, incomplete clinical or pathological staging, or missing data regarding radiation therapy were excluded from the analysis.

Variables and definitions

Demographic, clinical, and pathological data were collected, including age, sex, race, health insurance status, facility type, Charlson/Deyo score, date of diagnosis, tumor location, clinical T category (cT), clinical nodal status (cN), receipt of radiation therapy, type of surgical resection, margin status, tumor grade, tumor size, number of LNs examined (<16 vs. ≥16), regional treatment modality, and date of death or last known follow-up.

Patients with cN0/ypN0 were considered to have "natural N0," patients with cN+/ypN0 were considered to have "downstaged N0," and patients with ypN+ were considered to be "node-positive" regardless of cN status. OS was defined as the time between the date of surgery and the date of death. Patients who were still alive or were lost to follow-up were censored at the date of last known follow-up.

Statistical analysis

Differences in demographic, clinical, and pathological characteristics among the natural N0, downstaged N0, and node-positive cohorts were compared using Fisher's exact tests or χ^2 tests where appropriate. The OS of natural N0, downstaged N0, and node-positive patients was estimated using the Kaplan-Meier method and evaluated using the log-rank test. Pairwise comparisons were performed between individual curves. A P-value of <0.05 was considered statistically significant.

To identify the factors associated with nodal downstaging, cN+ patients were analyzed to determine the ypN0 status outcome. Propensity-score matching was used to reduce the risk of selection bias. The matching criteria were limited to preoperative factors and included age,

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sex, race, tumor location, facility type, year of diagnosis, and clinical T stage. Postoperative and pathological factors were not included in the propensity-score matching, as these factors are subject to influence by preoperative treatment. NACR patients were matched to NAC patients in a 1:1 ratio using the nearest-neighbor method (calipers of width 0.2*standard deviation, without replacement) [22]. Univariable and multivariable conditional logistic regression analyses were applied to the matched cohort to assess the relationship between clinicopathological variables and ypN0 status. Each factor was run in a univariable model and retained if P<0.25; stepwise selection was performed to build the final multivariable model. OS in the matched cN+ cohort was estimated using the Kaplan-Meier method, stratified by preoperative therapy and ypN status, and compared using the log-rank test. A P-value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA).

RESULTS

A total of 7426 patients with gastric cancer who met all inclusion criteria were identified (**Supplementary Fig. 1**). **Table 1** describes the characteristics of the entire study population as well as the natural N0, downstaged N0, and node-positive cohorts. The study population was predominantly male (76.9%), less than 65 years of age (61.3%), and white (79.6%). The most common tumor location was the cardia (69.0%). The cN status was positive in 60.5% of patients, and those who had received NACR and NAC accounted for 58.2% and 41.8% of the cohort, respectively. Approximately half of the patients (3,755 [50.6%]) had persistent lymph-node-positive disease (ypN+) after resection (cN+/ypN+: n=2,682 [36.1%] and cN0/ypN+: n=1,073 [14.4%]). Of those with ypN0, 1,858 were categorized as having natural N0 (25.0%), and 1.813 were categorized as having downstaged N0 (24.4%). There were significant differences among the cohorts in nearly all characteristics. Notably, downstaged N0 patients

Table 1. Characteristics of natural N0 (cN0/ypN0), downstaged N0 (cN+/ypN0), and node-positive (ypN+) gastric cancer patients

Characteristic	Total (n=7,426)	Natural N0 (n=1,858)	Downstaged N0 (n=1,813)	ypN+ (n=3,755)	P-value
Age (yr)					<0.001
≤65	4,553 (61.3)	1,053 (56.7)	1,099 (60.6)	2,401 (63.9)	
>65	2,873 (38.7)	805 (43.3)	714 (39.4)	1,354 (36.1)	
Sex					<0.001
Male	5,711 (76.9)	1,379 (74.2)	1,457 (80.4)	2,875 (76.6)	
Female	1,715 (23.1)	479 (25.8)	356 (19.6)	880 (23.4)	
Race or ethnicity					<0.001
White	5,908 (79.6)	1,503 (80.9)	1,504 (83.0)	2,901 (77.3)	
Black	621 (8.4)	144 (7.8)	130 (7.2)	347 (9.2)	
Hispanic	520 (7.0)	123 (6.6)	94 (5.2)	303 (8.1)	
Asian or Pacific Islander	312 (4.2)	77 (4.1)	67 (3.7)	168 (4.5)	
Other or unknown	65 (0.9)	11 (0.6)	18 (1.0)	36 (1.0)	
Insurance					<0.001
Private insurance	3,622 (48.8)	835 (44.9)	903 (49.8)	1,884 (50.2)	
Not insured	187 (2.5)	42 (2.3)	25 (1.4)	120 (3.2)	
Government plan	3,540 (47.7)	956 (51.5)	873 (48.2)	1,711 (45.6)	
Unknown	77 (1.0)	25 (1.4)	12 (0.7)	40 (1.1)	
Facility type					<0.001
Community cancer program	339 (4.6)	95 (5.1)	69 (3.8)	175 (4.7)	
Comprehensive community cancer program	2,093 (28.2)	548 (29.5)	453 (25.0)	1,092 (29.1)	
Academic or research program	4,160 (56.0)	1,007 (54.2)	1,116 (61.6)	2,037 (54.3)	
Integrated network cancer program	834 (11.2)	208 (11.2)	175 (9.7)	451 (12.0)	

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Table 1. (Continued) Characteristics of natural N0 (cN0/ypN0), downstaged N0 (cN+/ypN0), and node-positive (ypN+) gastric cancer patients

Characteristic	Total (n=7,426)	Natural N0 (n=1,858)	Downstaged N0 (n=1,813)	ypN+ (n=3,755)	P-value
Charlson-Deyo score					0.978
0	5,374 (72.4)	1,336 (71.9)	1,314 (72.5)	2,724 (72.5)	
1	1,637 (22.0)	417 (22.4)	401 (22.1)	819 (21.8)	
≥2	415 (5.6)	105 (5.7)	98 (5.4)	212 (5.7)	
Year of diagnosis					<0.001
2004–2009	1,713 (23.1)	433 (23.3)	359 (19.8)	921 (24.5)	
2010–2014	5,713 (76.9)	1,425 (76.7)	1,454 (80.2)	2,834 (75.5)	
Tumor location					<0.001
Cardia	5,122 (69.0)	1,262 (67.9)	1,440 (79.4)	2,420 (64.5)	
Body or fundus	961 (12.9)	245 (13.2)	173 (9.5)	543 (14.5)	
Antrum or pylorus	674 (9.1)	198 (10.7)	105 (5.8)	371 (9.9)	
Overlapping	355 (4.8)	68 (3.7)	49 (2.7)	238 (6.3)	
NOS	314 (4.2)	85 (4.6)	46 (2.5)	183 (4.9)	
cT category					<0.001
T0/IS/1	550 (7.4)	249 (13.4)	91 (5.0)	210 (5.6)	
T2	1,471 (19.8)	494 (26.6)	329 (18.2)	648 (17.3)	
T3	4,963 (66.8)	1,036 (55.8)	1,313 (72.4)	2,614 (69.6)	
T4	442 (6.0)	79 (4.3)	80 (4.4)	283 (7.5)	
cN status					<0.001
Negative	2,931 (39.5)	1,858 (100.0)	-	1,073 (28.6)	
Positive	4,495 (60.5)	-	1,813 (100.0)	2,682 (71.4)	
Preoperative radiation therapy					<0.001
No	3,105 (41.8)	748 (40.3)	518 (28.6)	1,839 (49.0)	
Yes	4,321 (58.2)	1,110 (59.7)	1,295 (71.4)	1,916 (51.0)	
Type of resection					<0.001
Near-total or total gastrectomy	945 (12.7)	226 (12.2)	167 (9.2)	552 (14.7)	
Partial or subtotal gastrectomy	1,933 (26.0)	571 (30.7)	448 (24.7)	914 (24.3)	
Gastrectomy with partial esophagectomy	3,660 (49.3)	881 (47.4)	1,018 (56.2)	1,761 (46.9)	
Other gastrectomy	888 (12.0)	180 (9.7)	180 (9.9)	528 (14.1)	
Tumor margin					<0.001
R0	6,477 (87.2)	1,717 (92.4)	1,719 (94.8)	3,041 (81.0)	
R1	491 (6.6)	67 (3.6)	51 (2.8)	373 (9.9)	
R2	22 (0.3)	2 (0.1)	3 (0.2)	17 (0.5)	
RX	436 (5.9)	72 (3.9)	40 (2.2)	324 (8.6)	
Tumor grade					<0.001
Well-differentiated	237 (3.2)	75 (4.0)	85 (4.7)	77 (2.1)	
Moderately differentiated	2,122 (28.6)	618 (33.3)	614 (33.9)	890 (23.4)	
Poorly differentiated	4,242 (57.1)	923 (49.7)	873 (48.2)	2,446 (65.1)	
Undifferentiated	106 (1.4)	25 (1.4)	18 (1.0)	63 (1.7)	
Unknown	719 (9.7)	217 (11.7)	223 (12.3)	279 (7.4)	
Tumor size					<0.001
<5 cm	4,059 (54.7)	1,080 (58.1)	967 (53.3)	2,012 (53.6)	
5–10 cm	1,454 (19.6)	263 (14.2)	348 (19.2)	843 (22.5)	
10–15 cm	186 (2.5)	24 (1.3)	24 (1.3)	138 (3.7)	
>15 cm	88 (1.2)	22 (1.2)	12 (0.7)	54 (1.4)	
Unknown	1,639 (22.1)	469 (25.2)	462 (25.5)	708 (18.9)	
No. of LNs examined					<0.001
<16	3,714 (50.0)	1,081 (58.2)	1,001 (55.2)	1,632 (43.4)	
≥16	3,619 (48.7)	748 (40.3)	784 (43.2)	2,087 (55.6)	
Unknown	93 (1.3)	29 (1.6)	28 (1.5)	36 (1.0)	
Any CXRT (preoperative or postoperative)					<0.001
No CXRT	2,636 (35.5)	691 (37.2)	481 (26.5)	1,464 (39.0)	
External beam	2,824 (38.0)	683 (36.8)	776 (42.8)	1,365 (36.4)	
Advanced CXRT	1,904 (25.6)	465 (25.0)	538 (29.7)	901 (24.0)	
NOS	62 (0.8)	19 (1.0)	18 (1.0)	25 (0.7)	

Values are presented as number of patients (%).
NOS = not otherwise specified; cT = clinical T category; cN = clinical nodal status; LN = lymph node; CXRT = chemoradiotherapy.

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were more likely than natural N0 patients to have tumors in the gastric cardia (79.4% vs. 67.9%, P<0.001) and to have a higher cT category (76.8% cT3-4 vs. 60.1% cT3-4, P<0.001).

OS

Over a median follow-up duration of 2.2 years, the median OS duration and 5-year OS rate were 3.0 years and 36.9% for the entire study population, 5.6 years and 52.4% for natural N0 patients, 5.1 years and 50.4% for downstaged N0 patients, and 2.1 years and 23.0% for node-positive patients, respectively. The Kaplan-Meier survival curves shown in **Fig. 1** demonstrate the markedly shorter survival of ypN+ patients relative to that of natural and downstaged N0 patients (P<0.0001, by log-rank test). A pairwise log-rank comparison of natural N0 and downstaged N0 patients confirmed that there was no difference between these 2 groups (P=0.2098).

Factors associated with nodal downstaging

A total of 4,495 patients were cN+, consisting of cN+/ypN0 (n=1,813, 40%) and cN+/ypN+ (n=2,682, 60%) (**Table 2**); of these, 1,753 received NAC, and 2,742 received NACR. There were significant differences in sex, race, tumor location, facility type, and cT category between the NAC and NACR groups. After propensity-score matching, 1,614 patients remained (807 in each group) who matched on all specified preoperative characteristics. The incidence of nodal downstaging (cN+/ypN0) was 30% for NAC and 47% for NACR patients (P<0.001) (**Fig. 2**). Additional postoperative differences between the NACR and NAC cohorts included R0 resection (90.8% vs. 82.9%, P<0.001), the percentage of poorly differentiated tumors (52.8% vs. 62.7%, P<0.001), and the percentage of patients with <16 lymph nodes examined (58.8% vs. 34.2%, P<0.001).

Table 3 shows the results of univariable and multivariable analyses of the matched cohort of cN+ patients with outcome ypN0 status. After multivariable regression, NACR was associated with a higher incidence of nodal downstaging than was NAC (odds ratio [OR], 2.02; 95% confidence interval [CI], 1.5–2.56; P<0.001). More recent diagnosis (2010–2014) was also associated with a higher incidence of nodal downstaging (OR, 2.57; 95% CI, 1.48–4.45; P<0.001). Tumor grade was significantly associated with outcome in the final model, indicating that poorly differentiated tumors are resistant to nodal downstaging (OR, 0.43; 95% CI, 0.30–0.62; P<0.001).

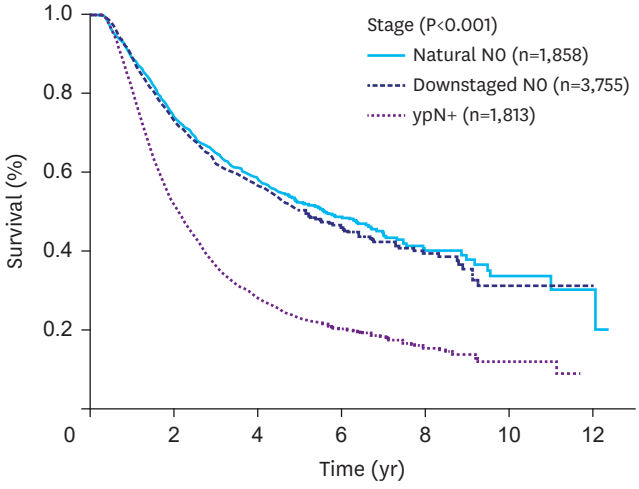

Fig. 1. OS of natural N0 (cN0/ypN0), downstaged N0 (cN+/ypN0), and node-positive (ypN+) patients.
OS = overall survival.

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Table 2. Characteristics of cN+ patients before and after 1:1 propensity-score matching, with and without preoperative CXRT

Characteristic	Total cN+ (n=4,495)	Before matching				After matching			
		NAC (n=1,753)	NACR (n=2,742)	P-value	Std. diff (%)	NAC (n=807)	NACR (n=807)	P-value	Std. diff (%)
Age (yr)				0.313	3.1			0.535	3.0
≤65	2,846 (63.3)	1,094 (62.4)	1,752 (63.9)			520 (64.4)	508 (63.0)		
>65	1,649 (36.7)	659 (37.6)	990 (36.1)			287 (35.6)	299 (37.0)		
Sex				<0.001	40.2			0.705	1.9
Male	3,566 (79.3)	1,215 (69.3)	2,351 (85.7)			649 (80.4)	655 (81.2)		
Female	929 (20.7)	538 (30.7)	391 (14.3)			158 (19.6)	152 (18.8)		
Race or ethnicity				<0.001	71.1			0.995	15.1
White	3,609 (80.3)	1,109 (63.3)	2,500 (91.2)			648 (80.3)	651 (80.7)		
Black	368 (8.2)	261 (14.9)	107 (3.9)			61 (7.6)	58 (7.2)		
Hispanic	291 (6.5)	217 (12.4)	74 (2.7)			60 (7.4)	62 (7.7)		
Asian or Pacific Islander	184 (4.1)	136 (7.8)	48 (1.8)			31 (3.8)	30 (3.7)		
Other or unknown	43 (1.0)	30 (1.7)	13 (0.5)			7 (0.9)	6 (0.7)		
Tumor location				<0.001	151.7			0.993	0.0
Cardia	3,262 (72.6)	666 (38.0)	2,596 (94.7)			660 (81.8)	661 (81.9)		
Body or fundus	527 (11.7)	464 (26.5)	63 (2.3)			66 (8.2)	63 (7.8)		
Antrum or pylorus	343 (7.6)	320 (18.3)	23 (0.8)			23 (2.9)	23 (2.9)		
Overlapping	200 (4.5)	172 (9.8)	28 (1.0)			25 (3.1)	28 (3.5)		
NOS	163 (3.6)	131 (7.5)	32 (1.2)			33 (4.1)	32 (4.0)		
Facility type				0.007	13.1			0.847	6.1
Community cancer program	188 (4.2)	61 (3.5)	127 (4.6)			33 (4.1)	38 (4.7)		
Comprehensive community cancer program	1,203 (26.8)	433 (24.7)	770 (28.1)			193 (23.9)	203 (25.2)		
Academic or research program	2,629 (58.5)	1,076 (61.4)	1,553 (56.6)			496 (61.5)	482 (59.7)		
Integrated network cancer program	475 (10.6)	183 (10.4)	292 (10.7)			85 (10.5)	84 (10.4)		
Year of diagnosis				0.405	2.5			0.821	1.1
2004–2009	1,019 (22.7)	386 (22.0)	633 (23.1)			215 (26.6)	211 (26.1)		
2010–2014	3,476 (77.3)	1,367 (78.0)	2,109 (76.9)			592 (73.4)	596 (73.9)		
cT category				<0.001	31.0			0.395	4.9
T0/IS/1	187 (4.2)	82 (4.7)	105 (3.8)			29 (3.6)	43 (5.3)		
T2	741 (16.5)	309 (17.6)	432 (15.8)			139 (17.2)	139 (17.2)		
T3	3,284 (73.1)	1,173 (66.9)	2,111 (77.0)			585 (72.5)	569 (70.5)		
T4	283 (6.3)	189 (10.8)	94 (3.4)			54 (6.7)	56 (6.9)		
Nodal status				<0.001	-			<0.001	-
ypN+	2,682 (59.7)	1,235 (70.5)	1,447 (52.8)			565 (70.0)	425 (52.7)		
ypN0	1,813 (40.3)	518 (29.5)	1,295 (47.2)			242 (30.0)	382 (47.3)		

Values are presented as number of patients (%).
CXRT = chemoradiotherapy; NAC = neoadjuvant chemotherapy; NACR = neoadjuvant chemoradiation; std. diff = standardized difference; NOS = not otherwise specified; cT = clinical T category.

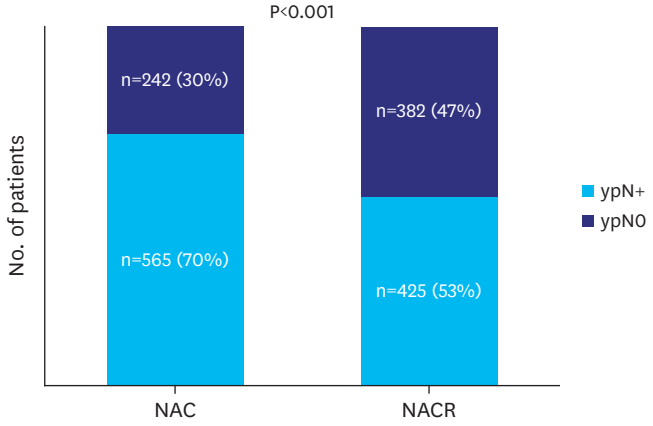

Fig. 2. Bar graph of the propensity-score-matched cohort of cN+ patients. The relative proportions of ypN+ and ypN0 (nodal downstaged) patients in the NAC and NACR groups are shown.
NAC = neoadjuvant chemotherapy; NACR = neoadjuvant chemoradiation.

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Table 3. Factors associated with nodal downstaging among 1,614 cN+ patients matched 1:1 by NACR to NAC (univariable and multivariable conditional logistic regression for outcome ypN0)

Characteristic	OR	95% CI	P-value
Univariable analysis			
Age (yr)			0.279
≤65		Reference	
>65	1.24	0.84–1.83	
Sex			0.916
Male		Reference	
Female	1.02	0.68–1.55	
Race			0.430
White		Reference	
Black	1.49	0.76–2.92	
Hispanic	1.94	0.84–4.52	
Asian or Pacific Islander	1.49	0.51–4.42	
Other or unknown	0.50	0.05–5.16	
Facility type			0.267
Community cancer program		Reference	
Comprehensive community cancer program	1.09	0.43–2.76	
Academic or research program	1.64	0.64–4.18	
Integrated network cancer program	1.06	0.39–2.85	
Charlson-Deyo score			0.469
0		Reference	
1	1.04	0.73–1.49	
≥2	0.66	0.33–1.32	
Year of diagnosis			0.004
2004–2009		Reference	
2010–2014	1.96	1.24–3.12	
Tumor location			0.717
Cardia		Reference	
Body or fundus	0.92	0.04–9.20	
Antrum or pylorus	0.28	0.02–5.47	
Overlapping	0.77	0.04–13.25	
NOS	0.50	0.05–5.51	
cT category			0.021
T0/IS/1		Reference	
T2	0.81	0.38–1.72	
T3	0.89	0.43–1.83	
T4	0.27	0.10–0.73	
Preoperative radiation therapy			<0.001
No		Reference	
Yes	2.12	1.71–2.62	
Type of resection			0.017
Near-total or total gastrectomy		Referencze	
Partial or subtotal gastrectomy	2.33	1.32–4.08	
Gastrectomy with partial esophagectomy	1.68	1.04–2.72	
Other gastrectomy	1.32	0.75–2.35	
Margin			<0.001
R0		Reference	
R1/2	0.17	0.09–0.34	
RX	0.22	0.09–0.52	
Grade			<0.001
Well- or moderately differentiated		Reference	
Poorly or undifferentiated	0.44	0.32–0.62	
Unknown	1.26	0.68–2.32	
Tumor size (cm)			0.004
<5		Reference	
5–10	0.86	0.60–1.25	
10–15	0.25	0.07–0.90	
>15	1.17	0.23–5.94	
Unknown	1.74	1.20–2.53	

(continued to the next page)

https://doi.org/10.5230/jgc.2020.20.e29

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Table 3. (Continued) Factors associated with nodal downstaging among 1,614 cN+ patients matched 1:1 by NACR to NAC (univariable and multivariable conditional logistic regression for outcome ypN0)

Characteristic	OR	95% CI	P-value
No. of LNs examined			<0.001
<16		Reference	
≥16	0.58	0.43–0.77	
Unknown	0.58	0.20–1.65	
pT category			<0.001
T0/TIS		Reference	
T1	0.11	0.04–0.33	
T2	0.05	0.02–0.14	
T3	0.03	0.01–0.08	
T4	0.01	0.01–0.01	
Multivariable analysis			
Grade			<0.001
Well- or moderately differentiated		Reference	
Poorly or undifferentiated	0.43	0.30–0.62	
Unknown	1.23	0.63–2.39	
Year of diagnosis			<0.001
2004–2009		Reference	
2010–2014	2.52	1.50–4.23	
Preoperative radiation therapy			<0.001
No		Reference	
Yes	2.09	1.67–2.62	

cN = clinical nodal status; NAC = neoadjuvant chemotherapy; NACR = neoadjuvant chemoradiation; OR = odds ratio; CI = confidence interval; NOS = not otherwise specified; cT = clinical T category; LN = lymph node; pT = pathologic T category.

OS of cN+ patients

In the matched cohort of cN+ patients, there was no significant difference in the median OS duration between patients who had received NAC versus NACR (2.72 vs. 2.74 years) (**Fig. 3A**). The survival of downstaged N0 and ypN+ patients in the matched cohort was estimated by the Kaplan-Meier method and stratified by the preoperative regimen (**Fig. 3B**). Patients who had received NACR had a shorter survival duration than did those who had received NAC (P=0.003, log-rank test). Patients who were downstaged by NAC had a median OS duration

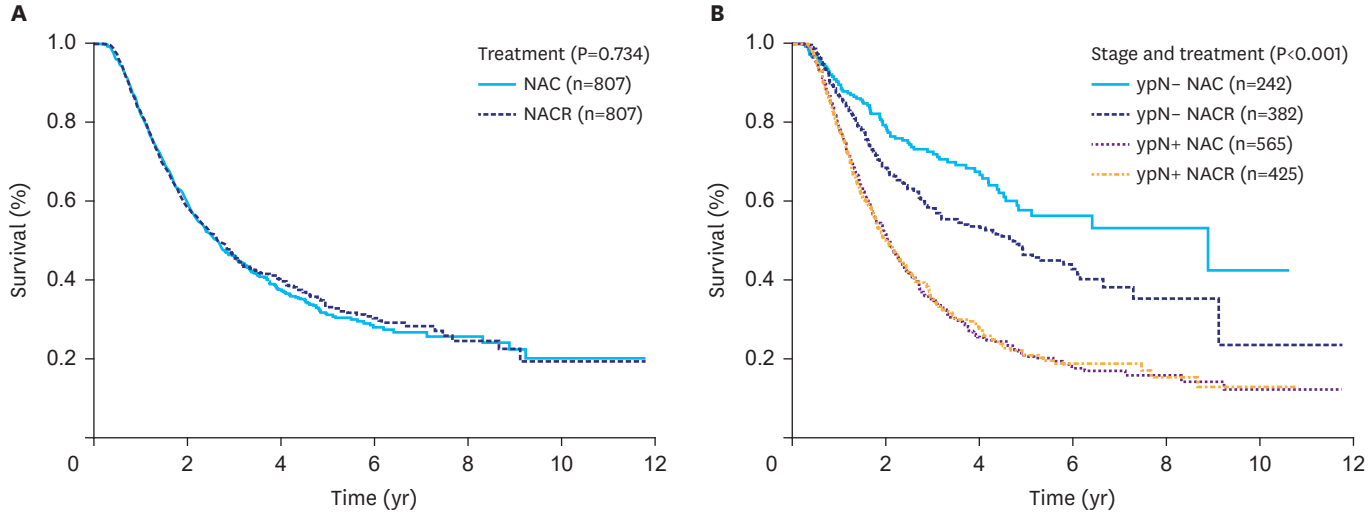

Fig. 3. (A) OS of the propensity-score-matched cN+ cohort, stratified by preoperative regimen. (B) OS of downstaged N0 and ypN+ patients in the matched cohort, stratified by preoperative regimen.
OS = overall survival; NAC = neoadjuvant chemotherapy; NACR = neoadjuvant chemoradiation.

https://doi.org/10.5230/jgc.2020.20.e29

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of 8.9 years and a 5-year survival rate of 57.7%; those downstaged by NACR had a median OS duration of 4.7 years and 5-year survival rate of 46.4%. Patients with ypN+ had similar OS durations and 5-year survival rates after NAC and NACR (2.04 vs. 2.01 years, 20.6% vs. 20.9%).

DISCUSSION

This retrospective cohort study of gastric cancer patients reported to the NCDB found that patients with nodal downstaging had the same OS as did those with natural node-negative disease, validating the results of the present group's previous report [20]. Equivalent survival between downstaged N0 and natural N0 patients was achieved despite the former having more advanced clinical stage disease, including both advanced cT stage and cN+ disease. Patients with ypN0 had excellent OS regardless of clinical stage; thus, the results of this study confirm the primary importance of ypN status in determining prognosis in patients with resectable gastric cancer who undergo preoperative therapy.

This group's previous work and the current study emphasize the validity of nodal downstaging as a treatment goal in gastric cancer. The prognostic significance of nodal downstaging may be specific to gastric cancer. For patients with esophageal adenocarcinoma, Zanoni et al. [23] demonstrated in a retrospective cohort (n=87) that the OS of downstaged N0 patients was significantly shorter than that observed for natural N0 patients. They determined that the benefit associated with ypN0 status was predicated on the simultaneous achievement of ypT0, a finding that is at odds with those of the current study and previous reports [19]. The difference between the results reported by Zanoni et al. [23] and those of the present group is likely a result of fundamental differences in the biology and behavior of nodal disease in patients with gastric and esophageal cancer. The latter may be a more aggressive entity, occurring earlier and being more frequently associated with a significant burden of distal disease. However, it is clear that in both esophageal and gastric cancer patients, ypN+ status is associated with poor prognosis, even in the setting of ypT0 [18,23,24]. For patients with pancreatic ductal adenocarcinoma, achievement of ypN0 after neoadjuvant therapy has been shown to confer a survival advantage over patients with ypN+ disease, but it is not clear whether this advantage occurs irrespective of clinical stage [25].

The analysis of the factors associated with nodal downstaging revealed two major independent, treatment-related factors that were predictive of ypN0: year of diagnosis and NACR. Improved efficacy of chemotherapy regimens and radiation therapy over the study period may have increased the incidence of ypN0 among patients who were treated in more recent years. The MAGIC trial regimen of epirubicin, cisplatin, and fluorouracil was established in 2006 as a perioperative regimen for gastric cancer and was widely adopted [3]. However, a phase II and III randomized trial established the superiority of docetaxel, oxaliplatin, leucovorin, and fluorouracil over epirubicin, cisplatin, and fluorouracil as a perioperative regimen, exhibiting greater pathological response to therapy and increased OS [26,27]. Regimens such as FOLFOX (leucovorin, fluorouracil, and oxaliplatin) and those with docetaxel in combination with cisplatin and fluorouracil have also shown efficacy in the perioperative setting [28,29]. As a result, it is likely that the agents used for preoperative chemotherapy have changed over time, with more recent patients receiving regimens with increased efficacy with regards to pathological response. This may be reflected in the increased rate of ypN0 seen in patients diagnosed 2010–2014. This will be important to keep in mind when the results of TOPGEAR are reported, as the choice of epirubicin,

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cisplatin, and fluorouracil as the regimen for the NAC arm may underestimate the benefit of chemotherapy alone.

This group's previous report using institutional data on nodal downstaging was poorly suited for investigating the role of radiation therapy, as it lacked an adequate comparison cohort [20]. In the current study, 61% underwent NACR, and the remainder underwent NAC. cN+ patients who had received NACR were twice as likely to achieve ypN0 as those who had not, confirming that NACR has a stronger impact on nodal downstaging than does NAC. This study therefore adds to the growing body of literature associating NACR with pathological downstaging—both of the primary tumor and of the regional lymph node basin. This group has previously shown that NACR induces ypT0 more frequently than does NAC [16]. NACR has been associated with high degrees of pathological complete response in prospective and small phase II clinical trials [13,30,31]. Stahl et al. conducted a randomized clinical trial of 119 locally advanced gastroesophageal junction tumors in which patients undergoing NACR were more likely than those receiving NAC to achieve a pathological complete response (15.6% vs. 2.0%, respectively) and have tumor-free lymph nodes (64.4% vs. 36.7%) [32]. They did not, however, examine the relationship between cN and ypN status. Finally, a recent analysis of the NCDB demonstrated that NACR is more likely than NAC to result in both a complete and partial pathological response in patients with gastroesophageal junction tumors [33].

No randomized data exist to document the presence or absence of a survival benefit attributable to NACR over NAC for patients with resectable gastric cancer. Two forthcoming clinical trials will address this question: TOPGEAR, in which patients with resectable gastric cancer will receive MAGIC regimen perioperative chemotherapy, with or without preoperative chemoradiotherapy (CXRT); and CRITICS-II, which will randomly assign patients to one of three arms, including preoperative chemotherapy, preoperative chemotherapy plus CXRT, and preoperative CXRT alone [8,9]. To date, no published retrospective data have convincingly demonstrated a survival benefit of NACR, despite the frequent correlation of NACR with surrogates of prognosis, including increased rates of pathological complete response.

The data presented in the current study may provide a mechanism to explain this disconnect. In a cohort of cN+ patients matched on key preoperative characteristics in a 1:1 ratio, OS was shorter if ypN0 was achieved after NACR. In other words, NACR induces nodal downstaging more frequently than does NAC, but the survival benefit of nodal downstaging may be greater when achieved by the latter. The proportion of patients achieving a pathological response may be greater after NACR than after NAC, but the aggregate OS in NACR- and NAC-treated patients is similar because the survival benefit associated with pathological response is greater after NAC. The present results show that nodal downstaging should be considered a hallmark of successful preoperative therapy, but they also demonstrate that the survival implication of nodal downstaging can differ by treatment regimen. Unique ypTNM-staging categories are needed for patients undergoing NACR and NAC to improve survival prediction.

There are a few possible explanations for the discrepancy in survival between downstaged N0 patients treated with NACR versus NAC. This observation is derived from a sub-group analysis of the propensity-score-matched cohort, and it is possible that persistent selection bias was not accounted for by the propensity-score-matching algorithm. However, patients were well-matched with regard to critical factors that are commonly associated with the selection of radiation therapy (such as cT category). Moreover, the OS of the cN+ cohort did not differ between NACR and NAC, indicating that the two treatment cohorts were well-

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balanced. A more likely explanation is the nature of radiation therapy as a local treatment modality. In patients receiving NACR, nodal downstaging may be attributable to the local effects of radiation therapy and not necessarily to the concurrently administered systemic therapy. In contrast, nodal downstaging after NAC represents the sole effect of systemic therapy, one to which all distant and micrometastatic disease was similarly exposed. It is therefore possible that the local effects of radiation therapy are predominantly responsible for ypN0 status in the NACR cohort and that distant and micrometastatic disease in these patients is either undertreated or resistant to therapy.

This study is subject to a number of limitations, including those related to its retrospective design and secondary nature. As discussed above, there is an inherent selection bias that may not be fully accounted for by the propensity-score-matching algorithm. There were also some differences between the matched cohorts. For instance, patients who had received NACR were less likely to have had 16 lymph nodes examined. In general, fewer lymph nodes examined can lead to stage migration and risks an overestimate of ypN0 incidence in the NACR cohort. However, having fewer lymph nodes removed after NACR may be an effect of the treatment itself, as was previously shown [34]. The current data do not clearly differentiate patients who received traditional external beam radiation therapy from those who received more advanced radiation techniques (intensity-modulated radiation therapy, volumetric-modulated arc therapy). The latter may have a different effect on outcome than that reported here, and caution should be exercised when extrapolating these results. Patients in this study had a high incidence of gastric cardia tumors; as a result, these findings may not be representative of gastric body tumors. However, the results are nonetheless relevant given the increasing incidence of gastric cardia tumors and decreasing incidence of non-cardia gastric tumors [35]. The adoption of nodal downstaging as a key objective of preoperative therapy may be limited by inaccuracy in clinical nodal staging [36]. In patients with esophageal cancer, assessing the "pretreatment pathological N-stage" by examining the extent of tumor regression in treated lymph nodes has been shown to be better correlated with prognosis than the conventional cN stage is [37]. However, for gastric cancer patients in whom ypN0 status indicates excellent survival regardless of cN stage, the clinical utility of such an approach may be minimal.

In conclusion, the results of this large multi-institutional cohort confirm the prognostic significance of nodal downstaging in patients with resectable gastric adenocarcinoma. Downstaged N0 patients have a prognosis similar to that of natural N0 patients; nodal downstaging therefore constitutes an important hallmark of successful preoperative therapy. Although NACR induces nodal downstaging more frequently than does NAC, the OS of patients downstaged by NACR is shorter than that of those downstaged by NAC. This highlights the disparity between pathologic response and OS and indicates a need for unique ypTNM staging categories for patients who receive preoperative regimens, including radiation therapy, compared with those who receive chemotherapy alone.

SUPPLEMENTARY MATERIAL

Supplementary Fig. 1

Flowchart demonstrating the selection of study cohorts from the NCDB.

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