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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Nodal Downstaging in Gastric Cancer Patients: Promising Survival if ypN0 is Achieved

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ABSTRACT

Background. The American Joint Committee on Cancer's 8th edition introduced ypStage, a separate staging system for patients with gastric cancer having undergone preoperative therapy. Overall, ypN0 patients have better survival outcomes than ypN+ patients. However, whether patients with cN+/ypN0 disease ("downstaged N0") and those with cN0/ypN0 disease ("natural N0") have similar survival is unknown.

Methods. An institutional database was reviewed to identify gastric adenocarcinoma patients who underwent potentially curative R0 resection after induction chemotherapy or chemoradiation. Patients were categorized into three groups based on nodal status: cN0/ypN0, cN+/ypN0, and ypN+. Univariable and multivariable Cox regression models were used to identify clinicopathologic factors associated with overall survival (OS).

Results. We identified 316 patients who met the study criteria. Ninety-four patients (30%) had cN0/ypN0 disease, 93 (29%) had cN+/ypN0 disease, and 129 (41%) had ypN+ disease. The median OS was 7.7 years, and the 5-year OS was 60.3%. In the multivariate analysis, OS did not differ between the cN0/ypN0 and cN+/ypN0 patients (hazard ratio, 0.90 [95% CI 0.54–1.48]; $p = 0.666$), but it was shorter in ypN+ patients (hazard ratio, 1.82 [95% CI 1.15–2.87]; $p = 0.01$).

Conclusions. In gastric cancer patients who underwent preoperative therapy, we found similar OS in cN0/ypN0 and cN+/ypN0 patients. Because ypN+ patients had poor OS, achieving ypN0 status is an important hallmark demonstrating the effectiveness of preoperative therapy for gastric cancer.

Gastric cancer treatment has undergone a shift from surgery alone to multimodality therapy over the past decade.[1,2] Most notably, after the MAGIC trial demonstrated a significant survival benefit of perioperative chemotherapy, the use of preoperative chemotherapy for gastric cancer has increased substantially. More than half of patients in the United States with T2-4Nany gastric cancer have undergone preoperative chemotherapy in recent years.[3] Currently, the international phase 3 Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma (TOPGEAR trial) is comparing perioperative chemotherapy (MAGIC regimen) with perioperative chemotherapy plus preoperative chemoradiation to identify the best perioperative therapy regimen for gastric cancer.[4] This shift of gastric cancer treatment to preoperative therapy necessitated a change in the American Joint Committee on Cancer staging manual. In the 8th edition, the committee introduced the novel ypStage system for gastric cancer patients who undergo preoperative therapy followed by gastrectomy.[5] Our analysis of ypStage for

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gastric cancer patients given preoperative therapy at The University of Texas MD Anderson Cancer Center, ypStage demonstrated reasonable survival prediction based on TNM grouping, whereas clinical stage (cStage) was not helpful.[6] Furthermore, we observed that ypN0 patients had markedly better overall survival than did ypN+ patients regardless of ypT category.[6] However, whether the survival of patients with clinically positive nodal disease before preoperative therapy, or "downstaged N0" disease (cN+/ypN0), is similar to that in those with "natural N0" disease (cN0/ypN0) is unknown. Therefore, we retrospectively investigated the impact of cN status on survival in gastric cancer patients with ypN0 disease after preoperative therapy and curative-intent gastrectomy.

METHODS

This study was conducted after obtaining MD Anderson Institutional Review Board approval of the protocol (PA13-0168). A prospectively maintained database of gastric cancer patients at department of Surgical Oncology was queried. Patient selection and variables collected were similar to those in a previous study by our group.[6] Patients with nonmetastatic primary gastric adenocarcinoma, including Siewert type III gastroesophageal tumors, who underwent potentially curative gastrectomies after chemotherapy or chemoradiation were included. The patient and tumor characteristics collected were age, sex, race/ethnicity, primary tumor location, cT category, cN status, ypT category defined according to the 8th edition of the American Joint Committee on Cancer staging manual, and histologic grade. cN status (negative vs. positive) was determined mainly via endoscopic ultrasound (EUS) performed by experienced endoscopists at our facility; computed tomography findings were used in cases in which EUS was not performed or not diagnostic ($n = 28$). Treatment variables consisted of use of preoperative radiation therapy, type of resection, concomitant organ resection, extent of lymph node dissection, number of lymph nodes examined, and postoperative chemotherapy. Preoperative chemotherapy and chemoradiation techniques have been previously described.[6–8] Patients were categorized into three groups based on nodal status: cN0/ypN0 (natural N0), cN+/ypN0 (downstaged N0), and ypN+.

Statistical Analysis

Kaplan–Meier methods were used to create survival curves for the study patients. Univariable and multivariable Cox regression models were fit to examine associations of variables with overall survival (OS). Factors with p values < 0.10 according to univariable analysis were included in the primary multivariable model. Stepwise methods with backward elimination were then used to create the final model.[9–11] Nodal status was kept in the model because it was the main exposure in this study. p values < 0.05 were considered statistically significant. All statistical analyses were conducted using the Stata 14.1 software program (StataCorp, College Station, TX).

RESULTS

We identified 316 patients who met the study criteria, including 74 patients (23%) with gastroesophageal junction tumors. Fifty-six percent of the patients were white, and 62% were male (Table 1). Two hundred thirty-nine patients (76%) underwent preoperative chemoradiation. Ninety-four patients (30%) had cN0/ypN0 disease, 93 (29%) had cN+/ypN0 disease, and 129 (41%) had ypN+ disease. Over a median follow-up duration of 3.1 years, 136 patients (43%) died. The median OS duration was 7.7 years, and the 5-year OS was 60.3%. OS did not differ between the cN0/ypN0 (5-year OS, 72%) and cN+/ypN0 (5-year OS, 69%) patients ($p = 0.776$; Fig. 1), even though the cN+/ypN0 group had more advanced baseline cT disease than the cN0/ypN0 group ($p < 0.001$). By multivariate analysis with adjustment for other factors, including ypT category, OS did not differ between cN0/ypN0 and cN+/ypN0 patients (hazard ratio, 0.90 [95% CI 0.54–1.48]; $p = 0.666$), but it was shorter in ypN+ patients (hazard ratio, 1.82 [95% CI 1.15–2.87]; $p = 0.01$; Table 2). Sensitivity analyses also demonstrated equivalent OS in the cN0/ypN0 and cN+/ypN0 patients in the ypT0-2 group ($p = 0.936$) and ypT3-4 group ($p = 0.608$; Fig. 2).

DISCUSSION

In this retrospective, single-institution study of gastric cancer patients who underwent preoperative therapy and curative-intent gastrectomy, we found that ypN status is a significant prognostic factor for survival. Also, we found no survival difference between cN0/ypN0 and cN+/ypN0 patients. With our previous finding of ypT0-3N0 patients having similar OS, these results demonstrated that ypN0 status is an important hallmark representing a successful preoperative treatment of gastric cancer regardless of pretreatment cN status.[6]

As described above, our previous study demonstrated uniformly good survival in ypN0 patients regardless of ypT category.[6] This finding motivated us to conduct the present study to identify a prognostic factor for survival in ypN0 patients. We initially considered cN status to be the factor. However, our present results demonstrated that cN status was not predictive of survival. This indicated that if

TABLE 1 Patient and tumor characteristics

Variable	No. of patients (%)			*p* value
	Natural N0 ($n = 94$)	Downstaged N0 ($n = 93$)	ypN+ ($n = 129$)	
Age $\geq$ 65 year	41 (44)	32 (34)	55 (43)	0.358
Male sex	53 (56)	63 (68)	80 (62)	0.278
Race/ethnicity				
White	51 (54)	52 (56)	73 (57)	0.725
Black	7 (7)	12 (13)	11 (9)	
Asian	9 (10)	10 (11)	16 (12)	
Hispanic/Latino	27 (29)	19 (20)	29 (22)	
Histology				
Well differentiated	1 (1)	0	0	0.154
Moderately differentiated	25 (27)	24 (26)	23 (18)	
Poorly differentiated	59 (63)	65 (70)	97 (75)	
Unknown	9 (10)	4 (4)	9 (7)	
Linitis plastica				
Yes	1 (1)	2 (2)	5 (4)	0.683
Suspicious	3 (3)	4 (4)	3 (2)	
Tumor location				
GEJ	16 (17)	29 (31)	29 (22)	0.168
Cardia/fundus	7 (7)	12 (13)	13 (10)	
Body	50 (53)	36 (39)	66 (51)	
Antrum	21 (22)	16 (17)	21 (16)	
Type of resection				
Total gastrectomy	37 (39)	57 (61)	72 (56)	0.010
Subtotal gastrectomy	54 (57)	30 (32)	51 (40)	
Proximal gastrectomy	3 (3)	6 (6)	6 (5)	
Preoperative radiation therapy	71 (76)	84 (90)	84 (65)	< 0.001
Postoperative chemotherapy	11 (12)	9 (10)	31 (24)	0.006
Concomitant organ resection	10 (11)	18 (19)	21 (16)	0.245
Extent of LN dissection = D1+/D2	78 (83)	84 (90)	112 (87)	0.335
$\geq$ 16 LNs examined	66 (70)	68 (73)	95 (74)	0.840
90-day postoperative mortality	4 (4)	1 (1)	2 (2)	0.269
cT category				
2	28 (30)	6 (6)	13 (10)	< 0.001
3/4a	63 (67)	74 (80)	107 (83)	
4b	3 (3)	13 (14)	9 (7)	
cN status				
Negative	94	0	48 (37)	NA
Positive	0	93	81 (63)	
ypT category				
0	20 (21)	29 (31)	7 (5)	< 0.001
1a/1b	30 (32)	14 (15)	12 (9)	
2	17 (18)	21 (23)	27 (21)	
3	22 (23)	22 (24)	64 (50)	
4a/b	4 (4)	2 (2)	16 (12)	
4b	1 (1)	5 (5)	3 (2)	

GEJ gastroesophageal junction, *LN* lymph node, *NA* not available

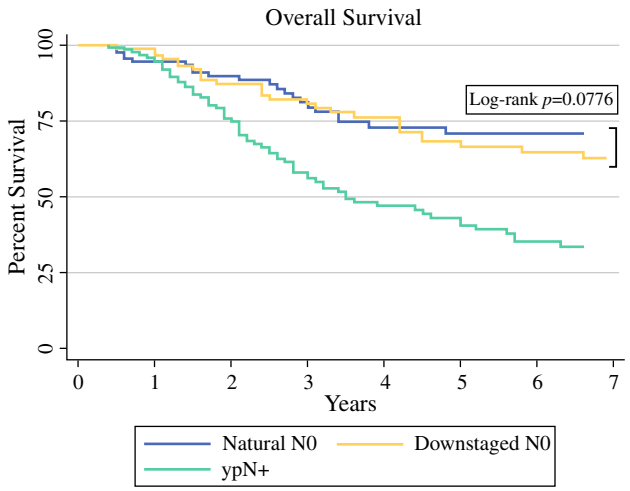

FIG. 1 Overall survival after diagnosis of cN0/ypN0 (natural N0), cN+/ypN0 (downstaged N0), and ypN+ patients

preoperative therapy can downstage node-positive disease to node-negative disease, that can result in excellent survival similar to that in naturally node-negative patients. In addition, the present study suggests that cStage has limited utility in survival prediction for gastric cancer patients who undergo preoperative therapy, indicating that we may be able to omit EUS from routine clinical practice. To our knowledge, the literature contains no other previous reports of this topic in gastric cancer. However, Zanoni et al. retrospectively studied 83 patients with cT2-4 esophageal cancer (42 adenocarcinomas and 41 squamous cell carcinomas) who underwent chemoradiation followed by surgical resection.[12] They reported that downstaged N0 patients had considerably inferior survival than did natural N0 patients (3-year OS rate, 59% vs. 84%). They concluded that downstaged N0 patients had to achieve a complete responses (ypT0N0) to benefit from preoperative chemoradiation.[12] The difference in the survival implications of cN status between the study by Zanoni and colleagues and ours is likely explained by differences between esophageal and gastric cancer, because esophageal cancer is more aggressive and has a wider lymphatic drainage pattern, and cN+ status may indicate more advanced disease than in gastric cancer patients. In addition, heterogeneity of the histology included in Zanoni et al. study (adenocarcinoma and squamous cell carcinoma) makes comparison of these two studies difficult.

Use of preoperative chemotherapy for gastric cancer has increased significantly over the past decade, but the best preoperative therapy regimen, particularly, whether chemoradiation provides better survival than chemotherapy alone does is currently under investigation.[3,4] The challenge in creating the ypStage system is heterogeneity of preoperative therapy regimens. Because pathologic downstaging may occur more frequently after more extensive preoperative therapy, particularly with intense chemoradition, survival prediction based on pathologic TNM findings likely differs according to the preoperative therapy regimen. In the present study, 76% of the patients underwent preoperative chemoradiation, whereas 24% underwent chemotherapy alone. Therefore, our study results maybe more representative of those who received chemoradiation, although sensitivity analyses conducted separately according to the regimen (chemoradiation and chemotherapy alone) had homogeneous results (data not shown), and we considered inclusion of all patients in this study to be reasonable. In the future, it may be beneficial to separate the ypStage system into different subsets based on preoperative therapy regimen (e.g., after chemoradiation, after chemotherapy). However, further clinical data are needed.

Our study was limited by the historically known inaccuracy of preoperative evaluation of cN status. Even intraoperative tactile assessment of nodes is reported to be inaccurate. A Japanese study of 522 patients with early-stage gastric cancer demonstrated a sensitivity rate of 32% and false-positive rate of 69% in intraoperative assessment of lymph node involvement, which also can be affected by histologic grade.[13,14] In addition, in a systematic review, Kwee et al. observed a wide range of reported sensitivity (16.7–96.8%) and specificity (48.4–100.0%) rates for EUS as well as sensitivity (62.5–91.9%) and specificity (50.0–87.9%) rates for computed tomography in evaluating lymph node status, showing that no modality consistently identifies N status in gastric cancer patients even in this era of advanced imaging technology.[15] Our institutional data on gastric cancer patients who underwent initial surgery after diagnostic imaging also demonstrated low accuracy in determining N status: 65% for computed tomography and 66% for EUS.[16] However, both modalities had very high specificity rates in detection of N+ disease (79% for computed tomography and 95% for EUS). Therefore, downstaged N0 patients in the present study highly likely had node-positive disease before initiation of preoperative therapy. Although a certain number of natural N0 patients may have had occult node-positive disease at presentation, we consider the comparison of the natural N0 and downstaged N0 patients to be valid. Moreover, because no other practical ways to provide accurate preoperative staging are available, we believe that these results are representative of general practice and are generalizable to other institutions.

This study has limitations associated with its retrospective nature, which resulted in some heterogeneity and possible selection bias regarding the preoperative staging modality and preoperative therapy regimen. Also, restricting the study to a single institution may have limited the generalizability of the results. Limited number of patients

TABLE 2 Univariable and multivariable Cox regression analysis of OS

Variable	Univariable		Multivariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
cN/ypN status				
Natural N0 (ref)	–	–	–	–
Downstaged N0	1.09 (0.67–1.76)	0.737	0.90 (0.54–1.48)	0.666
ypN+	2.07 (1.35–3.17)	**0.001**	1.82 (1.15–2.87)	**0.010**
ypT category				
0	1.65 (0.88–3.09)	0.118	2.03 (1.06–3.88)	0.032
1 (ref)	–	–	–	–
2	1.53 (0.82–2.82)	0.178	1.74 (0.92–3.27)	0.087
3	2.23 (1.26–3.95)	**0.006**	2.12 (1.17–3.86)	**0.014**
4a/b	3.30 (1.70–6.40)	< **0.001**	3.00 (1.49–6.04)	**0.002**
Age at diagnosis (≥ 65 vs. < 65 years)	1.51 (1.07–2.14)	**0.018**	1.39 (0.98–1.98)	0.066
Sex	0.67 (0.47–0.96)	**0.030**	–	–
Race/ethnicity				
White (ref)	–	–	–	–
Black	1.25 (0.69–2.25)	0.457	–	–
Asian	0.59 (0.32–1.08)	0.086	–	–
Hispanic	0.80 (0.53–1.23)	0.312	–	–
Tumor location (GEJ vs. other)	1.42 (0.98–2.05)	0.063	1.48 (1.00–2.18)	**0.049**
Histology (poorly vs. well/moderately differentiated)	0.94 (0.62–1.42)	0.768	–	–
Linitis plastica (yes/suspicious vs. no)	1.04 (0.51–2.13)	0.913	–	–
Concomitant organ resection	1.62 (1.08–2.44)	**0.019**	1.54 (1.00–2.36)	**0.048**
Type of resection				
Total gastrectomy (ref)	–	–	–	–
Subtotal gastrectomy	0.66 (0.46–0.94)	0.023	–	–
Proximal gastrectomy	0.75 (0.36–1.55)	0.434	–	–
Preoperative XRT	1.05 (0.69–1.58)	0.821	–	–
Adjuvant therapy	0.94 (0.59–1.52)	0.813	–	–
Number of LNs examined < 16	1.33 (0.93–1.88)	0.115	1.50 (1.05–2.15)	**0.027**

HR hazard ratio, *CI* confidence interval, *GEJ* gastroesophageal junction, *XRT* radiation therapy, *LNs* lymph nodes

p values < 0.05 are in boldface

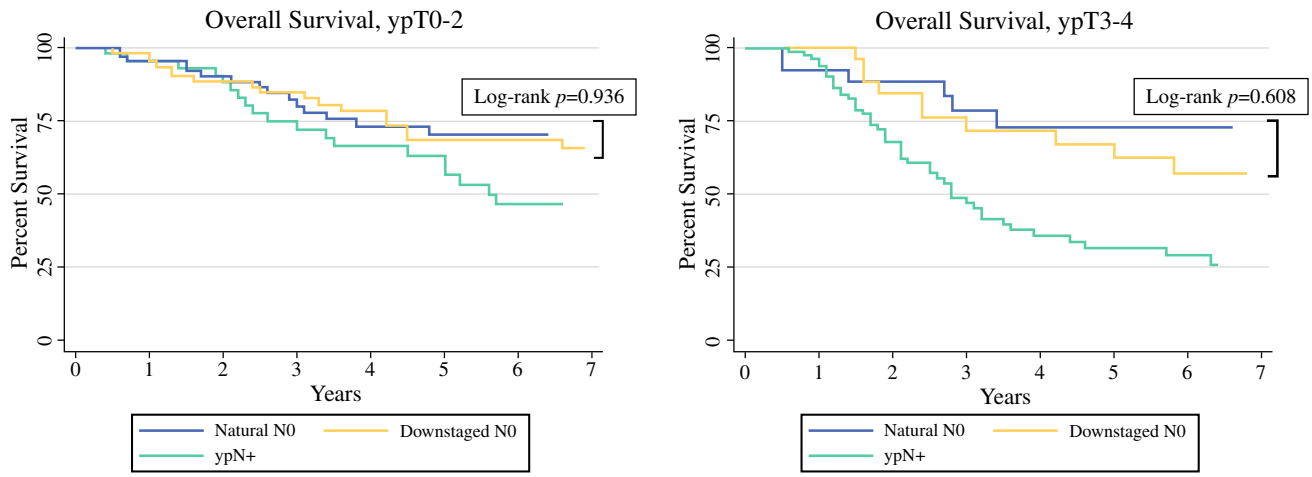

FIG. 2 Overall survival after diagnosis of cN0/ypN0 (natural N0), cN+/ypN0 (downstaged N0), and ypN+ patients, stratified by ypT category

is another limitation, which limited power to detect survival difference between cN0ypN0 and cN+/ypN0 patients. However, the standardized treatment/staging strategy improved the reliability of the study. Long follow-up time and uniform data quality are other strengths of the study, supported by a consistent institutional follow-up system. The analysis in and results of this study are novel and important for future developmenet of thestaging system for gastric cancer in this era of preoperative therapy for this cancer.

CONCLUSIONS

In patients with gastric cancer who underwent preoperative therapy, we found similar OS in cN0/ypN0 and cN+/ypN0 patients. Because ypN+ patients had poor OS, ypN0 status is an important hallmark demonstrating the effectiveness of preoperative therapy for gastric cancer, regardless of cN status.

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