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Further Classification for Node-Positive Gastric Neuroendocrine Neoplasms

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Abstract

Background For gastric neuroendocrine neoplasms (GNEN), the current AJCC lymph node (N) stage classifies patients into N0/N1 disease (with/without locoregional nodal metastases); however, this does not account for the number of involved nodes. The objective of this study was to evaluate the prognostic significance of the number of involved locoregional nodes among resected GNEN.

Methods The National Cancer Database (2004–2014) was queried for GNEN patients who had undergone partial/total gastrectomy with known nodal status. Nearest-neighborhood grouping was used to identify survival clusters by number of metastatic nodes and to use these groupings to construct a new N classification (pN). External validation was performed using the SEER database. Kaplan-Meier analysis and Cox regression models were used to assess the prognostic strength of the pN classification.

Results One thousand two hundred seventy-five patients met study inclusion criteria. Patients with 1–6 positive nodes (pN1) demonstrated a distinct survival pattern from patients with > 6 positive nodes (pN2) as well as those with no positive nodes (N0) {5-year OS N0: 80% (95% CI 77–83%) vs. 65% (95% CI 61–69%) vs. 43% (95% CI 33–53%), $p < 0.001$}. On external validation, the pN classification demonstrated strong discriminatory ability for survival {5-year OS N0: 70% (95% CI 65–75%) vs. pN1:53% (95% CI 46–59%) vs. pN2:18% (95% CI 9–29%), $p < 0.001$}. On multivariable analysis, the pN classification remained an independent predictor of OS.

Conclusions The number of metastatic lymph nodes is an independent prognostic factor in GNEN. Current AJCC N1 disease contains two groups of patients with distinctive prognoses, hence needs to be subclassified into pN1 (1–6 positive lymph nodes) and pN2 (> 6 positive nodes).

Keywords Gastric neuroendocrine neoplasm · Gastric carcinoid · Lymph nodes

Introduction

Gastric neuroendocrine neoplasms (GNENs) are derived from enterochromaffin-like cells in the gastric mucosa and account for 5–10% of all neuroendocrine neoplasms.[1,2] While the reported incidence of GNENs has increased significantly worldwide over the past several decades, GNENs are a rare neoplasm and the current state of knowledge of the natural history and optimal management remains limited.[3,4] Contributing to the difficulty in the management and understanding of GNENs is their heterogenous pathogenesis and presentation.[5–8] Three subtypes of GNENs have been defined by their association with hypergastrinemia and other disease conditions (type 1 with autoimmune atrophic gastritis, pernicious anemia; type 2 with Zollinger-Ellison syndrome; type 3 occurring sporadically) and range from relatively indolent to rapidly aggressive in progression.[9–11]

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Accordingly, treatment recommendations differ by subtype and are guided by the varying propensity for development of metastatic disease.[12] The National Comprehensive Cancer Network (NCCN) guidelines recommend surgical resection for all type 3 lesions, and type 1 and 2 lesions > 2 cm that are not amenable to endoscopic resection.[13] In comparison, the European Neuroendocrine Tumor Society (ENETS) recommends surgical resection only for type 1 lesions with invasion beyond the submucosa and of poor tumor differentiation, as well as for all type 2 lesions regardless of size and all type 3 lesions.[14] As a result, majority of resected GNENs consist of type 2 and 3 lesions. However, these patients still display significant heterogeneity in their long-term prognosis, with rates of tumor-related deaths ranging from < 10% for type II GNENs to 25–30% for type III GNENs.[14]

Given this significant heterogeneity in the clinical behavior and prognosis of GNENs, accurate staging is critical in determining appropriate patient treatment and in providing prognostic information for physicians to counsel patients. The current American Joint Commission on Cancer (AJCC) guidelines for the locoregional lymph node staging of GNENs classify nodal metastases as either absent or present (N0/N1).[15,16] This is contrary to the nodal staging criterion of nearly all other solitary tumors, including gastric adenocarcinoma, which are based on the number of metastatic lymph nodes.[16] Prior studies have reported the prognostic value of both lymph node ratio, defined as the number of positive lymph nodes divided by the number of total examined lymph nodes, as well as the absolute number of metastatic lymph nodes in other neuroendocrine neoplasms.[17–19] In a single-institution study consisting of 73 GNEN patients, both the number and ratio of metastatic lymph nodes were identified as independent predictors of survival.[20]

In this context, this study sought to examine the prognostic impact of the number of involved locoregional lymph nodes on overall survival in GNEN and to define cut-off values for the number of involved locoregional lymph nodes in order to better stratify patients' prognosis.

Methods

This was a retrospective, population-based study using data provided by the esophagogastric participant use file of the National Cancer Database (NCDB). The NCDB is a collaborative program between the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The NCDB currently captures 70% of newly diagnosed cancer cases in the USA and collects data from over 1500 CoC-accredited cancer hospitals.[21]

The NCDB was queried between 2004 through 2014 for all patients ≥ 18 years of age with GNEN histology of the primary tumor who had undergone partial or total gastrectomy with available lymph node information. GNENs were classified using the International Classification of Diseases for Oncology, 3rd Edition histology and behavior codes as well as the location of the primary tumor. Patients were excluded from analysis if they had less than a partial gastrectomy performed or had missing data on the number of positive lymph nodes. Disease staging was performed in accordance with the AJCC Staging System, 8th edition.[16] Overall survival (OS) was measured from the date of diagnosis to the date of death or last follow-up. Patient demographic, disease and treatment characteristics, and post-operative and long-term outcomes were abstracted from the NCDB for patients meeting inclusion criteria.

Nearest-neighborhood grouping was used to identify groups of patients with similar survival outcomes based on the number of involved locoregional lymph nodes. Patients were initially grouped into quintiles by the number of positive nodes. Kaplan-Meier survival analysis and the log-rank test were used to compare OS among the five groups. Groups with adjacent overlapping survival curves were combined in a stepwise fashion until a statistically significant difference by log-rank test was achieved among all curves. This final grouping based on the number of involved locoregional lymph nodes was used to develop a new proposed N classification (pN).

Clinical and treatment characteristics were compared between AJCC N0/N1 patients and by the pN classification using the chi-squared test for categorical variables and the student's t test for continuous variables to evaluate the distinct disease patterns of each subset. A Cox proportional-hazards model was used to evaluate the association between patient and disease characteristics and survival outcomes. The results of the multivariable analysis were presented as hazard ratios (HR) with the associated 95% confidence intervals (CI) and p values. A p value < 0.05 and a 95% CI exclusive of 1 were considered significant.

External validation of the pN classification system was performed using another population-based cancer registry, the Surveillance, Epidemiology, and End Results (SEER) database (1998–2013). The same inclusion and exclusion criteria were used to identify patients for the validation cohort. OS was measured from date of diagnosis to the date of death or last follow-up. Kaplan-Meier survival analysis and the log-rank test were used to evaluate OS.

Subgroup analysis of survival by T stage was evaluated using Kaplan-Meier survival analysis. All statistical analysis was performed using STATA software (v14.1, StataCorp, College Station, TX). This study was approved by the Partners Health Research Committee institutional review board.

Results

Study Population

Between 2004 and 2014, 1275 patients were identified in the NCDB who met study inclusion criteria. Fifty-four percent of

patients ($n = 688$) had zero involved locoregional lymph nodes (N0) and 46% ($n = 587$) had one or more involved lymph nodes (AJCC N1). The median number of positive lymph nodes was two nodes (range 1–32). Patients with positive nodal involvement tended to have tumors of larger size, of poor or undifferentiated grade, of higher T stage, with presence of lymphovascular invasion, and positive margins after resection (Table 1). Patients with positive lymph nodes also had more lymph nodes examined overall (median 11 vs. 6 nodes, $p < 0.001$).

Generation of New N Stage (pN1 and pN2) Based on Number of Involved Locoregional Lymph Nodes

Using nearest-neighborhood grouping, patients were initially divided into quintiles 1–5 by the number of involved locoregional lymph nodes (Supplemental Fig. 1a). For the first step in the nearest-neighborhood grouping, as there was no difference in OS among patients in quintiles 2, 3, and 4, these were subsequently combined into quintile 2′; patients in quintile 1 and 5 demonstrated distinct survival patterns from the other groups and were maintained as separate groups as quintile 1′ and 3′, respectively (Supplemental Fig. 1b). For the third step in the nearest-neighborhood grouping, patients in quintiles 1′ and 2′ did not have any significant differences in OS and were subsequently combined into quintile 1″; patients in quintile 3′ continued to demonstrate a distinct survival pattern and were maintained as a separate group, quintile 2″ (Supplemental Fig. 1c). In this final step, two groups with distinct survival patterns were identified among patients with nodal involvement, those with 1–6 positive nodes (quintile 1″) and those with > 6 positive nodes (quintile 2″). Patients with 1–6 positive nodes were designated as pN1 and patients with > 6 positive nodes were designated at pN2. Patients with zero positive lymph nodes (N0) had the highest 5-year OS of 79.7% (95% CI 76.5–82.5%), followed by pN1 patients with 65.0% (95% CI 60.6–69.1%), and then pN2 patients with 43.3% (95% CI 33.0–53.2%) (all $p < 0.001$) (Supplemental Fig. 1d).

Patient and Tumor Characteristics by pN Stage

Compared to patients with pN1 disease, patients with pN2 disease tended to have even larger tumors, more poorly/undifferentiated tumors, more T4 tumors, higher proportion with lymphovascular invasion present, and higher incidence of positive margins at resection (Table 2).

Stratification of Overall Survival with Proposed pN1 and pN2 Classification in NCDB

The OS of patients from the NCDB as stratified by current AJCC N staging guidelines is shown in Fig. 1a and the OS by the proposed N classification is shown in Fig. 1b. Patients with N0 disease had a 5-year OS of 79.7% (95% CI 76.5–82.5%). Patients with AJCC N1 disease had a 5-year OS of 61.3% (95% CI 57.3–65.1%). Using the pN classification, AJCC N1 patients from the NCDB can be further stratified into pN1 and pN2 with significantly different prognosis (5-year OS 65.0 vs. 43.3%, $p < 0.001$).

External Validation in SEER Database

The pN classification system also demonstrated strong discriminatory ability for patient survival outcomes on external validation using the SEER database. Between 1998 and 2013, 618 patients were identified from SEER who met study inclusion criteria, of whom 56% had zero lymph node metastases ($n = 344$) and 44% had ≥ 1 lymph node metastases ($n = 274$). Patients with N0 disease had 5-year OS of 70.4% (95% CI 65.2–74.9%) (Fig. 1c, d). By the AJCC classification, patients with N1 disease had 5-year OS of 46.4% (95% CI 40.4–52.1%). Within this group of patients from the SEER database, using the pN classification, patients with pN1 disease had 5-year OS of 52.9% (95% CI 46.2–59.2%) compared to 17.7% (95% CI 8.7–29.2%) for patients with pN2 disease ($p < 0.001$).

Stratification by T Stage

Subgroup analysis was performed to evaluate survival outcomes when patients were stratified by T stage (Fig. 2). From the NCDB, patients with T1, T2, and T4 primary tumors demonstrated distinct survival outcomes at 5-years using the pN classification system (T1: N0 89.9% {95% CI 83.8–93.8%}, pN1 82.6% {95% CI 60.1–93.1%}, pN2 median not reached, $p < 0.001$; T2: N0 80.1% {95% CI 74.7–84.4%}, pN1 72.2% {95% CI 65.6–77.7%}, pN2 65.0% {95% CI 40.3–81.5%}, $p = 0.034$; T4: N0 52.2% {95% CI 37.0–65.4%}, pN1 49.3% {95% CI 37.3–60.3%}, pN2 24.3% {95% CI 12.1–38.8%}, $p = 0.030$) (Fig. 2a, b, d). There was no statistically significant survival difference by pN stage among patients with T3 tumors (5-year OS N0 68.2% {95% CI 57.2–77.0%}, pN1 60.1% {95% CI 52.1–67.3%}, pN2 54.8% {95% CI 36.0–70.3%}, $p = 0.27$) (Fig. 2c).

From SEER, patients with T2 and T3 tumors had distinct 5-year survival outcomes when stratified by the pN classification system (T2: N0 76.3% {95% CI 67.4–83.1%}, pN1 69.3% {57.6–78.4%}, pN2 14.3% {95% CI 2.3–36.6%}, $p < 0.001$; T3: N0 67.3% {95% CI 67.4–83.1%}, pN1 69.3% {95% CI 57.6–78.4%}, pN2 14.3% {95% CI 2.3–36.6%}, $p = 0.009$) (Fig. 2f, g). Among patients with T1 tumors, there were no patients with pN2 disease available for analysis (Fig. 2e). There was no statistically significant difference in 5-year

Table 1 Comparison of patient demographics and disease characteristics between patients with N0 and N1 disease based on current AJCC 8th edition classification

	AJCC N0 $n = 688$	AJCC N1 $n = 587$	p value
Age, median (IQR)	61 (22–89)	61 (28–89)	0.44
Sex, male	301 (43.8%)	329 (56.1%)	*< 0.001*
Race			
White	543 (78.9%)	448 (76.3%)	0.53
Black	108 (15.7%)	98 (16.7%)	
Asian	20 (2.9%)	25 (4.3%)	
Other/Unknown	17 (2.5%)	16 (48.5%)	
Charlson/Deyo Score			
0	467 (67.9%)	413 (70.4%)	0.57
1	158 (23.0%)	128 (21.8%)	
2	63 (9.2%)	46 (7.8%)	
Tumor location			
Proximal	117 (23.1%)	102 (21.6%)	0.11
Body	119 (23.5%)	101 (21.4%)	
Distal	122 (24.1%)	105 (22.3%)	
Lesser curve	50 (9.9%)	77 (16.3%)	
Greater curve	58 (11.4%)	52 (11.0%)	
Overlapping	41 (8.1%)	35 (7.4%)	
Tumor size			
≤ 2 cm	392 (67.4%)	167 (30.4%)	*< 0.001*
2–4 cm	100 (17.2%)	173 (31.5%)	
4–6 cm	42 (7.2%)	101 (18.4%)	
> 6 cm	48 (8.3%)	108 (19.7%)	
Tumor differentiation			
Well	294 (42.7%)	185 (31.5%)	*< 0.001*
Moderate	55 (8.0%)	77 (13.1%)	
Poor	81 (11.8%)	158 (26.9%)	
Undifferentiated	14 (2.0%)	28 (4.8%)	
Unknown	244 (35.5%)	139 (23.7%)	
AJCC T classification			
T1	148 (27.4%)	23 (4.3%)	*< 0.001*
T2	261 (48.3%)	234 (41.6%)	
T3	85 (15.7%)	192 (34.1%)	
T4	46 (8.5%)	113 (20.1%)	
Number of positive LN, median (range)	0	2 (1–32)	*< 0.001*
Number of LN examined	6 (1–56)	11 (1–61)	*< 0.001*
Lymphovascular invasion present	50 (19.2%)	150 (60.0%)	*< 0.001*
Positive margin	52 (7.7%)	74 (12.9%)	*0.003*
Chromogranin level[a]	22 (0–980)	145 (0–980)	0.04
Mitotic count[b]	.1 (0–51)	.9 (0–51)	0.07

AJCC American Joint Committee on Cancer, *IQR* interquartile range, *cm* centimeter, *LN* lymph nodes

Italic indicates significant p values

[a] Chromogranin A level available for 65 N0 and 58 N1 patients

[b] Mitotic count available for 151 N0 and 104 N1 patients

OS among patients with T4 tumors when stratified by pN stage (N0 44.0% {95% CI 24.5–61.9%}, N1 31.9% {95% CI 19.3–45.3%}, N2 21.1% {95% CI 6.6–41.0%}, $p = 0.29$) (Fig. 2h).

Independent Prognostic Effect of pN System

On univariable analysis, increasing patient age, Charlson-Deyo score of 2, worsened tumor differentiation,

Table 2 Comparison of patient demographics and disease characteristics between patients with N0, N1, and N2 disease based on newly proposed N classification

	Proposed N0 classification $n = 688$	Proposed N1 classification $n = 486$	Proposed N2 classification $n = 90$	p value[a]
Age, median (IQR)	61 (22–89)	60 (29–89)	62 (35–84)	0.18
Sex, male	301 (43.8%)	269 (55.4%)	52 (57.8%)	0.67
Race				
White	543 (78.9%)	378 (77.8%)	61 (67.8%)	0.17
Black	108 (15.7%)	74 (15.2%)	22 (24.4%)	
Asian	20 (2.9%)	21 (4.3%)	4 (4.4%)	
Other/Unknown	17 (2.5%)	13 (2.7%)	3 (3.3%)	
Charlson/Deyo score				
0	467 (67.9%)	342 (39.3%)	61 (67.8%)	0.45
1	158 (23.0%)	109 (22.4%)	19 (21.1%)	
2	63 (9.2%)	35 (7.2%)	10 (11.1%)	
Tumor location				
Proximal	117 (23.1%)	81 (20.9%)	19 (24.7%)	0.55
Body	119 (23.5%)	78 (20.2%)	20 (26.0%)	
Distal	122 (24.1%)	88 (22.7%)	17 (22.1%)	
Lesser curve	50 (9.9%)	66 (17.1%)	10 (13.0%)	
Greater curve	58 (11.4%)	47 (12.1%)	5 (6.5%)	
Overlapping	41 (8.1%)	27 (7.0%)	6 (7.8%)	
Tumor size				
≤ 2 cm	392 (67.4%)	156 (34.3%)	8 (9.5%)	*< 0.001*
2–4 cm	100 (17.2%)	154 (33.9%)	18 (21.4%)	
4–6 cm	42 (7.2%)	70 (15.4%)	30 (35.7%)	
> 6 cm	48 (8.3%)	75 (16.5%)	28 (33.3%)	
Tumor differentiation				
Well	294 (42.7%)	166 (34.2%)	17 (18.9%)	*< 0.001*
Moderately	55 (8.0%)	67 (13.8%)	10 (11.1%)	
Poorly	81 (11.8%)	109 (22.4%)	45 (50.0%)	
Undifferentiated	14 (2.0%)	21 (4.3%)	6 (6.7%)	
Unknown	244 (35.5%)	123 (25.3%)	12 (13.3%)	
AJCC T classification				
T1	148 (27.4%)	23 (5.0%)	1 (1.1%)	*< 0.001*
T2	261 (48.3%)	212 (45.7%)	20 (22.5%)	
T3	85 (15.7%)	158 (34.1%)	31 (34.8%)	
T4	46 (8.5%)	71 (15.3%)	37 (41.6%)	
Number of positive LN, median (range)	0	2 (1–6)	10 (7–32)	*< 0.001*
Number of LN examined	6 (1–56)	10 (1–61)	18 (7–48)	*< 0.001*
Lymphovascular invasion present	50 (19.2%)	120 (56.3%)	28 (82.4%)	*0.004*
Positive margin	52 (7.7%)	52 (10.9%)	20 (23.3%)	*0.002*
Chromogranin level	22 (0–980)	88 (0–980)	200 (0–439)	0.52
Mitotic count	.1 (0–51)	.9 (0–51)	.9 (0–38)	0.42

IQR interquartile range, *cm* centimeter, *LN* lymph nodes

Italic indicates significant p values

[a] p values are calculated between proposed N1 and proposed N2 classification groups

increased T stage, AJCC N1 disease, pN1 and pN2 disease, increased number of involved lymph nodes, presence of lymphovascular invasion, and positive resection margin were associated with decreased OS. Female sex and tumor location outside of the proximal stomach was associated with improved OS. Adjusting for these factors

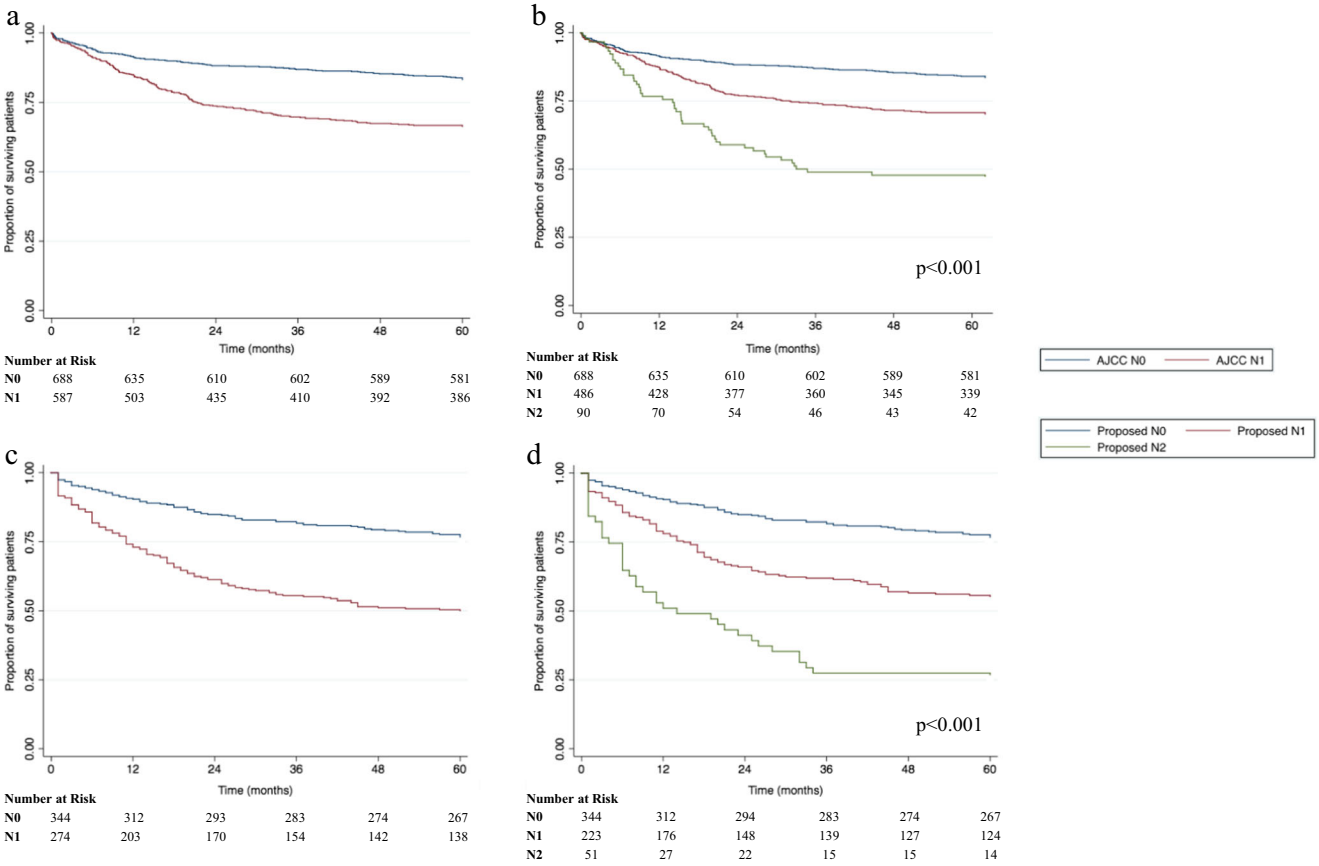

Fig. 1 Comparison of overall survival for patients with **a** AJCC N0 vs. N1 disease in NCDB training data set, **b** N0 vs. pN1 vs. pN2 disease in NCDB training data set, **c** AJCC N0 vs. N1 disease in SEER validation data set, and **d** N0 vs. pN1 vs. pN2 disease in SEER validation data set

on multivariable analysis, the pN classification remained significantly associated with OS (Table 3).

Discussion

The current AJCC nodal staging system classifies lymph node involvement as either present or absent lymph node metastases (N0/N1). However, GNEN patients currently categorized as AJCC N1 disease represent a highly heterogeneous group with broad variability in their survival outcomes. Appropriate and accurate staging is particularly critical in GNEN as this disease presents with significant variance in its clinical behavior and progression, ranging from indolent to aggressive pathophysiology. Detailed staging is also needed to provide precise prognostic information. In the present study, we demonstrate a significant difference in survival between patients with 1–6 involved locoregional lymph nodes (pN1) and those with > 6 involved nodes (pN2).

Patients who are currently classified by AJCC as N1 disease, which indicates the presence of any involved locoregional lymph nodes, demonstrate a broad range of survival outcomes. After stratifying these patients using the pN classification, we identified two distinct subgroups. Patients with 1–6 involved lymph nodes (pN1) had significantly improved 5-year OS compared to those with > 6 lymph nodes (pN2) {pN1 65% (95%CI 61–69%) vs. pN2 43% (95%CI 33–53%), $p < 0.001$}. As this latter group of pN2 patients comprised nearly 20% of patients with positive nodes, changes in staging guidelines harbor significant prognostic ramifications for an estimated one in five patients diagnosed with GNEN with nodal involvement. Prior single institution series have also suggested the prognostic significance of the number of involved locoregional lymph nodes in GNEN patients. In a series of 73 GNEN patients, Tang et al. demonstrated that the number of involved locoregional lymph nodes, as well as the lymph node ratio and station, was an independent predictor of survival.[20] In another series of 43 GNEN patients, Liu et al. also reported a significant association between the number of involved lymph nodes and survival and specifically identified seven lymph nodes as an important cut-off value to stratify survival (> 7 positive lymph nodes HR 2.766, 95% CI 1.101–6.948, $p = 0.030$).[22] This is similar to the present study where we identified a significant survival difference for patients with > 6 involved nodes. In addition to the number of involved lymph nodes, the significance of the lymph node ratio (LNR), defined as the proportion of positive lymph nodes among all examined nodes, has also been highlighted in

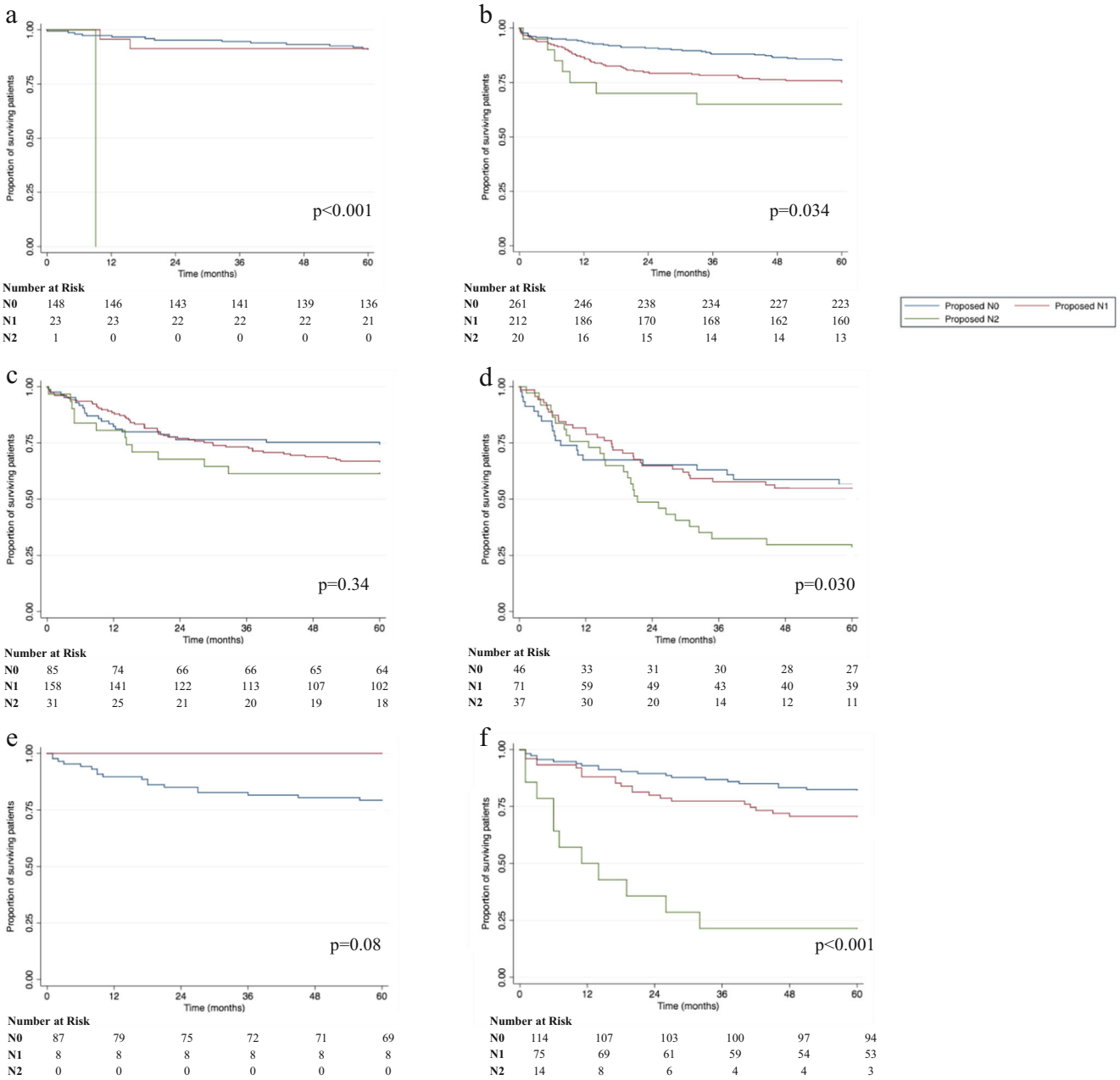

Fig. 2 Comparison of overall survival using the proposed N classification, stratified by T stage of primary tumor: **a** T1 in NCDB training data set, **b** T2 in NCDB training data set, **c** T3 in NCDB training data set, **d** T4 in NCDB training data set, **e** T1 in SEER validation data set, **f** T2 in SEER validation data set, **g** T3 in SEER validation data set, and **h** T4 in SEER validation data set

neuroendocrine neoplasms. Two prior population-based studies using the SEER database have demonstrated LNR as an independent predictor of survival in neuroendocrine neoplasms as a group and specifically in small intestine neuroendocrine neoplasms, with higher LNR associated with decreased survival.[17,19] Together, these results emphasize the prognostic impact of the number of involved lymph nodes on survival for patients with various types of neuroendocrine neoplasms.

The number of involved locoregional lymph nodes continued to demonstrate prognostic significance when patients were stratified by T stage, using both NCDB and SEER data (Fig. 2). Patients with tumors of higher T stage, indicating larger tumors with increased depth of invasion, often undergo more extensive resections, including a higher number of lymph nodes resected. This is also supported by the present study by the increasing number of lymph nodes examined among N0/pN1/pN2 patients (median 6 vs. 10 vs. 18 lymph nodes, $p < 0.001$). However, on subgroup analysis, the number of involved lymph nodes remained significantly associated with overall survival, independent of T stage. The lack

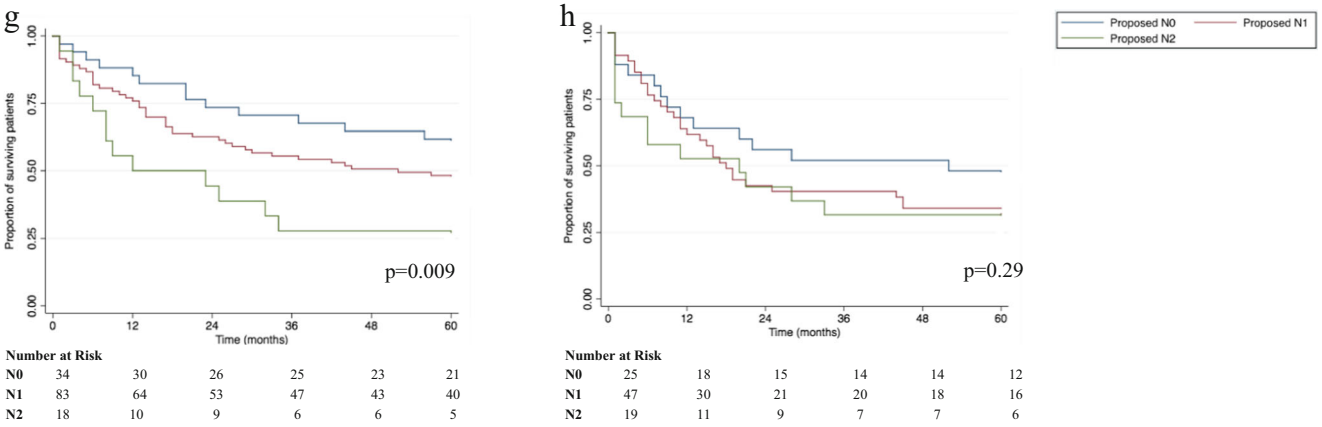

Fig. 2 (continued)

Table 3 Univariable and multivariable Cox regression analysis for overall survival

	Univariable			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.051	1.043–1.059	< 0.001	1.021	1.0003–1.043	*0.047**
Sex (Ref: Male)	0.585	0.491–0.696	< 0.001	0.476	0.278–0.813	*0.007*
Race (Ref: White)						
Black	1.219	0.974–1.527	0.08	–	–	–
Asian	1.306	0.804–2.123	0.28			
Other/Unknown	1.083	0.595–1.972	0.79			
Charlson/Deyo Score (Ref: 0)						
1	1.079	0.879–1.323	0.47	1.038	0.575–1.872	0.90
2	1.731	1.335–2.244	< 0.001	1.011	0.449–2.277	0.98
Tumor location (Ref: proximal)						
Body	0.522	0.387–0.704	< 0.001	0.435	0.194–0.976	*0.043*
Distal	0.809	0.611–1.071	0.14	1.103	0.579–2.101	0.77
Lesser curve	0.550	0.389–0.780	0.001	0.475	0.204–1.104	0.08
Greater curve	0.609	0.436–0.850	0.004	0.307	0.113–0.838	*0.021*
Overlapping	0.708	0.488–1.029	0.071	0.809	0.288–2.269	0.69
Tumor differentiation (Ref: Well/Mod)						
Poor/Undifferentiated	4.989	4.031–6.175	< 0.001	2.996	1.709–5.252	*< 0.001*
AJCC T classification (Ref: T1)						
T2	1.551	1.115–2.157	0.009	0.795	0.288–2.193	0.66
T3	3.212	2.278–4.531	< 0.001	0.806	0.278–2.340	0.69
T4	5.141	3.618–7.305	< 0.001	1.858	0.636–5.434	0.26
AJCC N classification (Ref: N0)						
N1	2.286	1.851–2.824	< 0.001	[a]-	–	–
Proposed N classification (Ref: N0)						
N1	1.995	1.594–2.497	< 0.001	2.065	1.056–4.039	*0.034*
N2	4.071	2.950–5.619	< 0.001	2.695	1.103–6.585	*0.030*
Number of positive LN	1.108	1.085–1.132	< 0.001	[a]-	–	–
Lymphovascular invasion present	3.848	2.719–5.446	< 0.001	1.551	0.909–2.646	0.11
Positive margin	1.527	1.184–1.968	0.001	1.370	0.633–2.966	0.42

HR hazard ratio, *CI* confidence interval, *Ref* reference value, *LN* lymph nodes

Italic indicates significant *p* values

[a] The variables AJCC N classification and number of positive lymph nodes was included in univariable analysis but excluded from multivariable analysis due to correlation with the variable proposed N classification

of a statistically significant difference among T3 patients from NCDB and T4 patients from SEER is likely due to limitations of sample size given the extreme rarity of GNEN.

The demonstration of the prognostic significance of number of involved lymph nodes in GNEN also impacts the development of future guidelines on the appropriate extent of lymphadenectomy. Current guidelines from the NCCN recommend regional lymph node resection, including all palpable disease, but does not specify a minimum lymph node harvest.[23] Similarly, the ENETS consensus guidelines also do not provide specific guidelines governing the extent of lymph node resection.[14] As the number of involved lymph nodes can vary depending on the number of lymph nodes resected, there is potential for understaging if an insufficient number of lymph nodes are examined.[24–26] Additional investigation is needed to determine the optimal number of lymph nodes that needs to be harvested and to develop recommendations on the appropriate extent of lymphadenectomy during resection for GNENs.

There are several limitations of this study. First, patients with missing lymph node information were excluded (n = 874) and there was no standardization in the extent or number of lymph nodes harvested. However, this reflects the reality of clinical practice, as currently there is no standard of care for lymph node resection in GNEN. Secondly, the NCDB does not capture Ki-67 index and only recorded mitotic count in a small minority of study patients. Both of these variables are needed to determine tumor grade, which is an important marker of tumor aggressiveness and prognostic factor in GNEN[6, 27]. Using the available variables, we included and adjusted for the differentiation grade in the multivariable analysis to demonstrate the continued prognostic significance of the number of positive lymph nodes. Third, we relied on overall survival as our survival measure as neither the cause of death nor disease-specific survival is captured by the NCDB.

Conclusions

The number of involved locoregional lymph nodes is an independent prognostic factor for patients with GNEN. Based on the current AJCC nodal classification, patients with N1 disease display significant heterogeneity in survival outcomes and should be staged with greater clinical granularity. Using two population-based cancer registries, the present study demonstrates the significant decrease in survival among patients with > 6 positive lymph compared to those with 1–6 positive nodes.

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Compliance with Ethical Standards

Disclosures The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

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