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ORIGINAL ARTICLE – COLORECTAL CANCER

Colon Neuroendocrine Tumors: A New Lymph Node Staging Classification

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ABSTRACT

Background. The American Joint Commission on Cancer, the European Neuroendocrine Tumor Society, and the North American Neuroendocrine Tumor Society all classify colon neuroendocrine tumor (NET) nodal metastasis as N0 or N1. This binary classification does not allow for further prognostication by the total number of positive lymph nodes. This study aimed to evaluate whether the total number of positive lymph nodes affects the overall survival for patients with colon NET.

Methods. The National Cancer Database was used to identify patients with colon NET. Nearest-neighborhood grouping was performed to classify patients by survival to create a new nodal staging system. The Surveillance, Epidemiology, and End Results database was used to validate the new nodal staging classification.

Results. Colon NETs were identified in 2472 patients. Distinct 5-year survival rates were estimated for the patients with N0 (no positive lymph nodes; 69.8%; 95% confidence interval [CI], 66.7–72.7%), N1a (1 positive lymph node; 63.9%; 95% CI, 59.6–68.0%), N1b (2–9 positive lymph nodes; 38.9%; 95% CI, 35.4–42.3%), and N2 ($\geq$ 10 positive lymph nodes; 15.7%; 95% CI, 11.9–20.0%; $p < 0.001$) nodal classifications. The validation population showed distinct 5-year survival rates with the new nodal staging. In multivariable Cox regression, the new nodal stage was a significant independent predictor of overall survival.

Conclusions. The number of positive locoregional lymph nodes in colon NETs is an independent prognostic factor. For patients with colon NETs, N0, N1a, N1b, and N2 classifications for nodal metastasis more accurately predict survival than current staging systems.

Gastroenteropancreatic neuroendocrine tumors (NETs) exhibit a wide range of tumor behavior depending on the tumor location. Colorectal NETs are the second most common NET in the gastrointestinal tract, with an annual incidence of approximately 0.3–1 per 100,000.[1,2]

Although colorectal NETs often are described as a single disease, colon NETs have a much worse prognosis than rectal NETs.[3–5] Furthermore, the incidence of colon NETs has increased during the past 40 years.[3,6]

Colon NETs have one of the lowest median survival rates of all NETs.[6] Although the 5-year survival rate for colon NETs localized to the colon is approximately 80%, it falls to less than 50% for tumors with metastasis to regional lymph nodes.[3,7]

For patients with distant metastasis, the 5-year survival rate is less than 10%, and the median survival period is only 5 months.[3,7,8] Important predictors of survival for patients with colon NETs include tumor size, depth of invasion, lymph node status, tumor grade, and the presence of metastatic disease.[3]

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In 2010, the American Joint Commission on Cancer (AJCC) developed a tumor-node-metastasis (TNM) staging classification for colon NETs. In this classification, lymph node metastasis is stratified into N0 (no regional nodal metastasis) or N1 (regional nodal metastasis) disease. In the recently updated 2017 AJCC 8th-edition staging manual, nodal metastasis continues to be categorized this way.[2] This nodal classification is in line with the staging advocated by the European Neuroendocrine Tumor Society (ENETS) and the North American Neuroendocrine Tumor Society (NANETS).[9,10] This binary staging system differs from nodal staging for other solid tumors such as colon adenocarcinomas, which have several categories stratified by the number of lymph nodes involved.[2]

Prior studies have demonstrated that the number of positive lymph nodes is associated with NET prognosis.[11–14] However, no studies to date have evaluated the independent prognostication for the number of positive lymph nodes in colon NETs.

This study aimed to evaluate whether the number of positive locoregional lymph nodes influences overall survival for colon NETs and to create a new nodal classification system that may provide patients with more accurate survival estimates.

MATERIALS AND METHODS

Data

Patient data were extracted from two databases: the National Cancer Database (NCDB) and the Surveillance, Epidemiology, and End Results (SEER) database. The NCDB, a clinical oncology database, jointly sponsored by the American Cancer Society and the American College of Surgeons, houses data from more than 1500 cancer centers in the United States and includes more than 34 million historical records.[15] Patient data, such as cancer stage, treatment, and survival, are acquired from hospital registries and collectively represent more than 70% of all new cancer diagnoses each year.

For this study, patient data from 2004 to 2015 was used. The SEER database then was used to validate the findings from NCDB. Supported by the National Cancer Institute's Surveillance Research Program, SEER provides information on cancer cases from various sources throughout the United States. Data are sourced from local registries in 19 U.S. geographic regions covering approximately one-third of the U.S. population.[16] Patient data from 2004 to 2015 was used. This study was reviewed and approved by the Partners Institutional Review Board.

Patient Population

Initial patient data were identified using the NCDB database and the International Classification of Diseases for Oncology codes. Patient demographics, tumor characteristics, and treatment method were extracted for patients older than 18 years who had a diagnosis of colon NETs and subsequently underwent bowel resection. Patients were excluded from the study if lymph node status was absent. Appendiceal and rectal carcinoid tumors were not included in the analysis. Subsequently, data from the SEER database were used to validate findings. The criteria for inclusion in the study were identical to those implemented for the NCDB patients.

Statistical Analysis

Appropriate statistical tests were used to compare patient data between the AJCC N0 and N1 groups in the NCDB database based on data diagnostics. For categorical variables, such as tumor differentiation or T classification, Fisher's exact tests or Chi square tests were used. For continuous variables, such as age or number of positive lymph nodes, two-sample independent *t* tests or Wilcoxon rank-sum tests were used. To analyze the correlation between survival and pertinent patient characteristics, a Cox proportional-hazards model was used. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported. For all tests, *p* values were assessed, with significance defined as a two-sided alpha lower than 0.05.

Nearest-neighborhood grouping was used to create distinct survival clusters of patients based on the number of positive lymph nodes. This statistical method has been used in prior work to create new staging classifications.[13,14] Initially, the NCDB data were used to create quintiles of patients with different ranges of positive lymph nodes (1 node, 2–3 nodes, 4–5 nodes, 6–9 nodes, $\geq$ 10 nodes). Survival outcomes among these groups were generated using Kaplan–Meier survival curves, and pairwise log-rank tests were performed. Groups that did not exhibit statistically significant differences in survival curves were combined until each different group of patients, based on the number of positive lymph nodes present, showed distinct survival curves and contained a reasonable number of patients to ensure model stability. The newly generated nodal staging classification is based upon these survival curves. Subsequently, the SEER data were analyzed using Kaplan–Meier survival curves and log-rank tests for external validation. All statistical analyses were conducted using Stata version 15 (StataCorp, College Station, TX, USA).

RESULTS

Overall NCDB Patient Population

The study identified 2472 patients who met the defined criteria in the NCDB (Table 1). Of these patients, 907 (36.7%) had no positive locoregional lymph nodes and comprised the AJCC N0 group, and 1565 patients (63.3%) had at least one positive locoregional lymph node and comprised the AJCC N1 group. The median number of positive lymph nodes in the AJCC N1 group was 4 (interquartile range [IQR], 1–8).

Patient age, gender, race, and Charlson/Deyo score did not differ significantly between the two groups (all $p > 0.05$). The tumors of the patients in the AJCC N1 group were significantly larger, were of a higher AJCC T stage, exhibited poorer differentiation, and were more likely to have lymphovascular invasion than the tumors of the patients in the AJCC N0 group (all $p < 0.05$).

Creation of a New Nodal Stage

Instead of using a binary scale to classify patients' lymph node status, the proposed nodal staging system separates patients into several distinct groups based on the number of positive lymph nodes. In each analysis, patient survival curves between groups were obtained and compared, and subsequently hierarchical clustering was

TABLE 1 Comparison of the 8th-edition AJCC N0/N1 patient characteristics in NCDB

Factor	AJCC N0 (0 positive LNs) (n = 907) n (%)	AJCC N1 (≥ 1 positive LNs) (n = 1565) n (%)	p value
Mean age (years)	62.7 ± 14.4	62.9 ± 12.5	0.67
Female	519 (57.2)	847 (54.1)	0.14
Race			0.65
White	757 (83.5)	1328 (84.9)	
Black	118 (13.0)	188 (12.0)	
Other	32 (3.5)	49 (3.1)	
Charlson/Deyo score			0.39
1	852 (93.9)	1456 (93.0)	
2	55 (6.1)	109 (7.0)	
Tumor size			< 0.001
< 1 cm or microscopic foci (cm)	246 (30.1)	87 (5.9)	
1–2	160 (19.6)	178 (12.0)	
2–4	198 (24.3)	588 (39.7)	
4–6	102 (12.5)	346 (23.4)	
> 6	110 (13.5)	281 (19.0)	
Tumor differentiation			< 0.001
Well differentiated	257 (28.3)	403 (25.8)	
Moderately differentiated	94 (10.4)	170 (10.9)	
Poorly differentiated	157 (17.3)	485 (31.0)	
Undifferentiated/anaplastic	38 (4.2)	121 (7.7)	
Missing	361 (39.8)	386 (24.7)	
AJCC T classification			< 0.001
1	230 (25.4)	78 (5.0)	
2	214 (23.6)	168 (10.7)	
3	367 (40.5)	847 (54.1)	
4	96 (10.6)	472 (30.2)	
Median no. of positive lymph nodes (IQR)	0.0 (0.0–0.0)	4.0 (1.0–8.0)	< 0.001
Median no. of examined lymph nodes (IQR)	12.0 (7.0–18.0)	15.0 (10.0–21.0)	< 0.001
Lymphovascular invasion present	75 (22.5)	516 (80.4)	< 0.001

AJCC American Joint Committee on Cancer, *NCDB* Nataional Cancer Database, *LN* lymph node, *IQR* interquartile range

modified until statistically significant differences in overall survival based on number of positive lymph nodes were elucidated.

In the first iteration, the patients were divided into quintiles based on the number of positive lymph nodes (1 node, 2–3 nodes, 4–5 nodes, 6–9 nodes, $\geq$ 10 nodes). Statistically significant differences were observed between groups 1 and 2 ($p < 0.001$), 1 and 3 ($p < 0.001$), and 4 and 5 ($p < 0.001$), but no significant difference was observed between groups 2 and 3 ($p = 0.16$) or 3 and 4 ($p = 0.07$). Thus, in the second iteration, quintiles 2, 3, and 4 were combined, resulting in three groups (1 node, 2–9 nodes, $\geq$ 10 nodes), later referred to respectively as N1a, N1b, and N2.

Statistically significant differences in overall survival were observed between groups N1a and N1b ($p < 0.001$), groups N1a and N2 ($p < 0.001$), and groups N1b and N2 ($p < 0.001$). Thus, the original AJCC N1 group was divided into three new, distinct groups. These groups were then compared with the AJCC N0 group (Table 2).

Overall Survival

Survival curves using the old N classification can be seen in Fig. 1a. The 5-year overall survival rate for the patients in the AJCC N0 group was 69.8% (95% CI, 66.7–72.7%), whereas it was 42.2% (95% CI, 39.8–44.7%) for the patients in the AJCC N1 group. Figure 1c shows the different survival curves using the new N classification, in which the original N1 group was subdivided into three groups. The patients in the new N1a group had a 5-year overall survival rate of 63.9% (95% CI, 59.6–68.0%), followed by the N1b group at 38.9% (95% CI, 35.4–42.3%), and subsequently by the N2 group at 15.7% (95% CI, 11.9–20.0%). Significant differences were observed for all pairwise comparisons (all $p < 0.05$).

SEER External Validation

Using the SEER database, the study extracted data for 2129 patients. Whereas 495 (23.3%) of the patients had no positive locoregional lymph nodes, 1634 (76.7%) had one or more positive lymph nodes. Figure 1b shows that the 5-year survival rate for the patients in the AJCC N0 group was 68.9% (95% CI, 64.6–72.8%), whereas for the patients in the AJCC N1 group, it was 51.2% (95% CI, 48.7–53.6%). The new nodal staging classification then was applied to these data. The patients in the N1a group had a 5-year overall survival rate of 59.9% (95% CI, 53.6–65.7%) compared with 56.5% (95% CI, 53.5–59.4%) for the patients in the N1b group and 22.4% (95% CI, 17.8–27.5%) for the patients in the N2 group (Fig. 1d). The survival differences were statistically significant for the N1a and N2 patients ($p < 0.001$), as well as for the N1b and N2 patients ($p < 0.001$), but not for the N1a or N1b patients ($p = 0.19$).

T Stage Stratification

The new nodal staging system then was analyzed in the context of T stage classification using both the NCDB and SEER data. For the NCDB data, the patients in the T1 stage group did not exhibit statistically significant differences in survival outcomes: N0 (80.0%; 95% CI, 74.2–84.6%), N1a (71.4% (95% CI, 58.6–80.9%), N1b (61.5% (95% CI, 30.8–81.8%), N2 (50.0%; 95% CI, 0.60–91.0%) ($p = 0.11$) (Fig. 2a). In contrast, distinct survival outcomes were seen for patients with T2, T3, and T4 tumors: T2: N0 (81.3%; 95% CI, 75.4–85.9%), N1a (76.6%; 95% CI, 67.4–83.6%), N1b (54.7%; 95% CI, 40.5–66.9%), N2 (62.5%; 95% CI, 22.9–86.1%) ($p < 0.0001$); T3: N0 (61.6%; 95% CI, 56.4–66.3%), N1a (64.1%; 95% CI, 57.5–69.9%), N1b (35.6%; 95% CI, 31.2–40.0%), N2 (16.6%; 95% CI, 11.4–22.6%) ($p < 0.0001$); T4: N0 (51.0%; 95% CI, 40.7–60.5%), N1a (44.9%; 95% CI, 34.9–54.4%), N1b (40.3%; 95% CI, 34.0–46.4%), N2 (11.3%; 95% CI, 6.6–17.3%) ($p < 0.0001$ (Fig. 2b–d).

The findings were similar for the SEER data. No statistically significant differences in survival outcomes were observed for the patients with T1 tumors: N0 (77.5%; 95% CI, 68.9–84.0%), N1a (67.9%; 95% CI, 47.3–81.8%), N1b (65.1%; 95% CI, 49.0–77.3%) ($p = 0.15$) (Fig. 2e). No patients in the N2 group had T1 tumors. However, significant differences were observed for the patients in the T2, T3 and T4 groups: T2: N0 (71.8%; 95% CI, 59.8–80.8%), N1a (65.3%; 95% CI, 50.3–76.8%), N1b (68.7%; 95% CI, 61.4–75.0%), N2 (29.2%; 95% CI, 13.0–47.6%) ($p < 0.0001$); T3: N0 (63.6%; 95% CI, 56.5–69.8%), N1a (60.7%; 95% CI, 51.0–69.1%), N1b (56.2%; 95% CI, 52.2–60.1%), N2 (21.4%; 95% CI, 15.3–28.2%) ($p < 0.0001$); T4: N0 (55.6%; 95% CI, 41.4–67.6%), N1a (50.0%; 95% CI, 36.1–62.4%), N1b (47.4%; 95% CI, 41.1–53.4%), N2 (21.8%; 95% CI, 14.3–30.2%) ($p < 0.0001$) (Fig. 2f–h).

New Nodal Staging as an Independent Predictor of Survival

Uni- and multivariable analyses were used to identify associations between predictor variables and overall survival (Table 3). A univariable analysis showed statistically significant associations between higher Charlson score, greater number of positive lymph nodes, poorer tumor differentiation, AJCC T stage classification of T3/T4, older age, higher AJCC N classification, positive resection margins, and the presence of lymphovascular invasion and

TABLE 2 Patient characteristics for proposed N0/N1/N2 patients in NCDB

	Proposed N0 (0 positive nodes) (n = 907) n (%)	Proposed N1a (1 positive node) (n = 499) n (%)	Proposed N1b (2–9 positive nodes) (n = 754) n (%)	Proposed N2 (≥ 10 positive nodes) (n = 312) n (%)	p value
Mean age (years)	62.7 ± 14.4	62.8 ± 12.6	62.1 ± 12.5	65.0 ± 12.4	0.01
Female	519 (57.2)	284 (56.9)	402 (53.3)	161 (51.6)	0.19
Race					0.18
White	757 (83.5)	406 (81.4)	651 (86.3)	271 (86.9)	
Black	118 (13.0)	77 (15.4)	80 (10.6)	31 (9.9)	
Other	32 (3.5)	16 (3.2)	23 (3.1)	10 (3.2)	
Charlson/Deyo score					0.24
1	852 (93.9)	468 (93.8)	705 (93.5)	283 (90.7)	
2	55 (6.1)	31 (6.2)	49 (6.5)	29 (9.3)	
Tumor size					< 0.001
< 1 cm or microscopic foci (cm)	246 (30.1)	66 (14.0)	14 (2.0)	7 (2.4)	
1–2	160 (19.6)	111 (23.6)	58 (8.1)	9 (3.0)	
2–4	198 (24.3)	171 (36.3)	336 (47.2)	81 (27.3)	
4–6	102 (12.5)	69 (14.6)	179 (25.1)	98 (33.0)	
> 6	110 (13.5)	54 (11.5)	125 (17.6)	102 (34.3)	
Tumor differentiation					< 0.001
Well differentiated	257 (28.3)	173 (34.7)	193 (25.6)	37 (11.9)	
Moderately differentiated	94 (10.4)	48 (9.6)	93 (12.3)	29 (9.3)	
Poorly differentiated	157 (17.3)	98 (19.6)	225 (29.8)	162 (51.9)	
Undifferentiated/anaplastic	38 (4.2)	21 (4.2)	62 (8.2)	38 (12.2)	
Missing	361 (39.8)	159 (31.9)	181 (24.0)	46 (14.7)	
AJCC T classification					< 0.001
1	230 (25.4)	63 (12.6)	13 (1.7)	2 (0.6)	
2	214 (23.6)	107 (21.4)	53 (7.0)	8 (2.6)	
3	367 (40.5)	231 (46.3)	447 (59.3)	169 (54.2)	
4	96 (10.6)	98 (19.6)	241 (32.0)	133 (42.6)	
Median no. of positive lymph nodes (IQR)	0.0 (0.0, 0.0)	1.0 (1.0, 1.0)	5.0 (3.0, 7.0)	14.0 (11.0, 18.0)	< 0.001
Median no. of examined lymph nodes (IQR)	12.0 (7.0–18.0)	13.0 (7.0–18.0)	13.0 (10.0–19.0)	21.0 (15.0–28.5)	< 0.001
Lymphovascular invasion present	75 (22.5)	128 (65.3)	262 (85.6)	126 (90.0)	< 0.001

NCDB Nataional Cancer Database, *AJCC* American Joint Committee on Cancer, *IQR* interquartile range

decreased overall survival (all $p < 0.05$). In a multivariable cox regression model, excluding the AJCC nodal stage and the number of positive lymph nodes due to co-linearity, the new nodal staging of N1a, N1b, and N2 was independently associated with overall survival ($p = 0.03$, $p < 0.001$, and $p < 0.001$, respectively).

DISCUSSION

The goal of this study was to evaluate the relationship between the total number of positive lymph nodes and survival for patients with colon NET. This is the largest study to date to assess survival outcomes in colon NET. Currently, the AJCC, NANETS, and ENETS all classify lymph nodes for colon NETs as N0 (no positive lymph nodes) or N1 (≥ 1 positive lymph nodes).[2,9,10] We demonstrated that significant differences in survival exist among patients with no positive lymph nodes (N0), 1 positive lymph node (N1a), 2–9 positive lymph nodes (N1b), and 10 or more positive lymph nodes (N2), signifying the importance of the total number of positive lymph nodes in the staging of colon NETs. These findings have implications for future staging iterations and may provide more accurate survival estimates when surgical and medical oncologists provide prognostic information to patients.

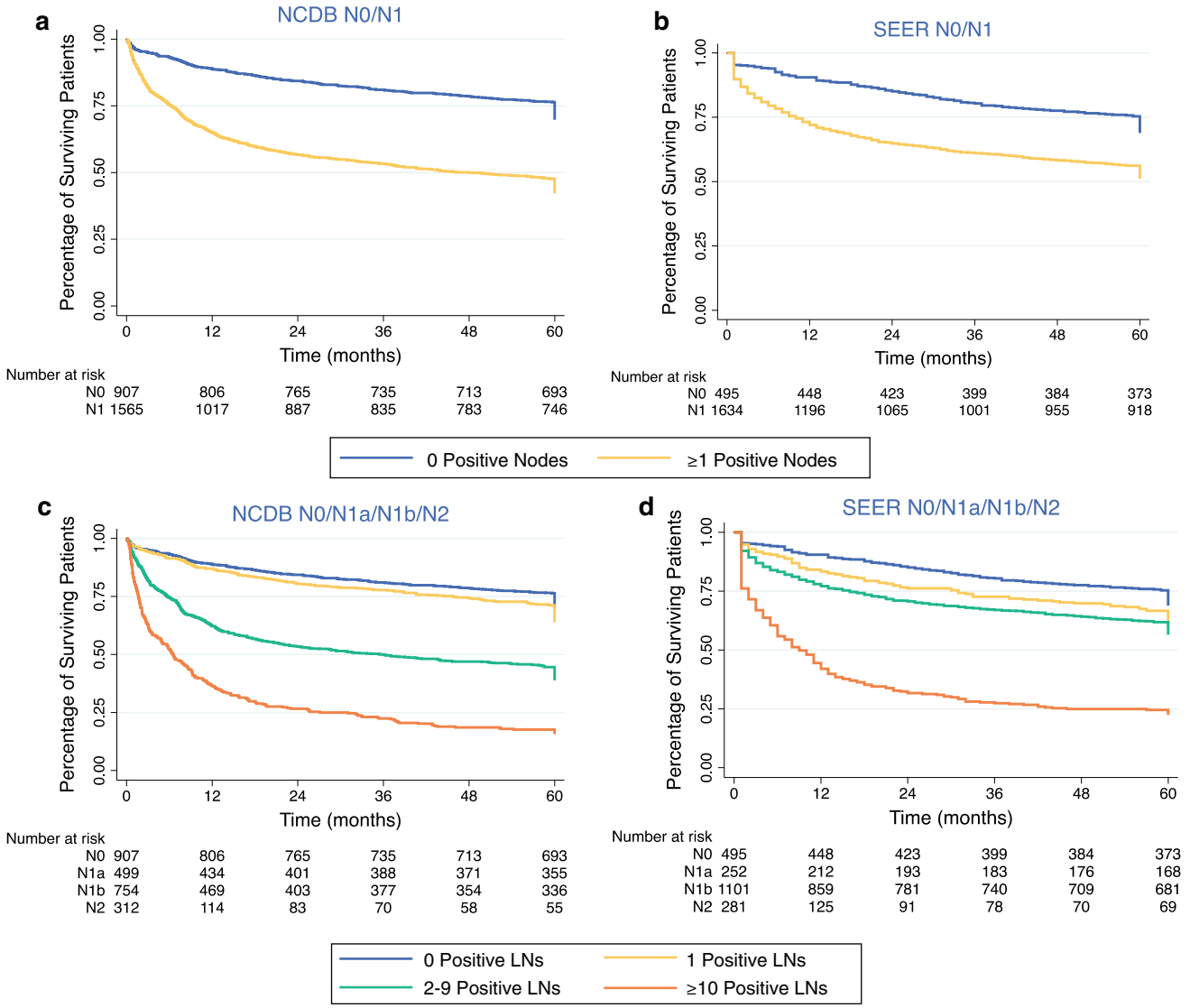

FIG. 1 Kaplan–Meier survival curves of new N classification compared to AJCC for SEER and NCDB

Patients with colon NETs have one of the lowest long-term survivals of all NETs.[6] The 5-year survival rate ranges from 10 to 80%, depending on the stage of disease.[3,7,8] For patients with positive locoregional lymph nodes, the 5-year survival rate typically is about 50%.[3,7]

In our study, the 5-year survival for N1 patients was 42.2% in NCDB and 51.2% in SEER, which is in agreement with prior reports. However, when patients are stratified by the total number of involved positive lymph nodes, survival outcomes spread considerably. In the NCDB data, the 5-year survival rate was 63.9% for patients with 1 positive lymph node (N1a), 38.9% for patients with 2–9 positive lymph nodes (N1b), and 15.7% for patients with 10 or more positive lymph nodes (N2).

Patients with a N1b or N2 nodal classification represent 69% of patients with positive lymph nodes in the NCDB data set. With the proposed new nodal classification, more than two of three patients with positive lymph nodes would be upstaged. In previous studies, lymph node metastasis had an impact on survival in colon NETs.[3] In other NETs, the number of positive lymph nodes and the lymph node ratio have been associated with survival outcomes.[11,13,14,17] These previously observed patterns support our findings in further stratification of lymph node status in colon NET patients.

After further stratification of patients by tumor stage, the new nodal staging remained a significant predictor of survival for patients in both national databases, independent of AJCC T stage. However, the T1 disease groups from both databases did not have distinct survival curves, likely

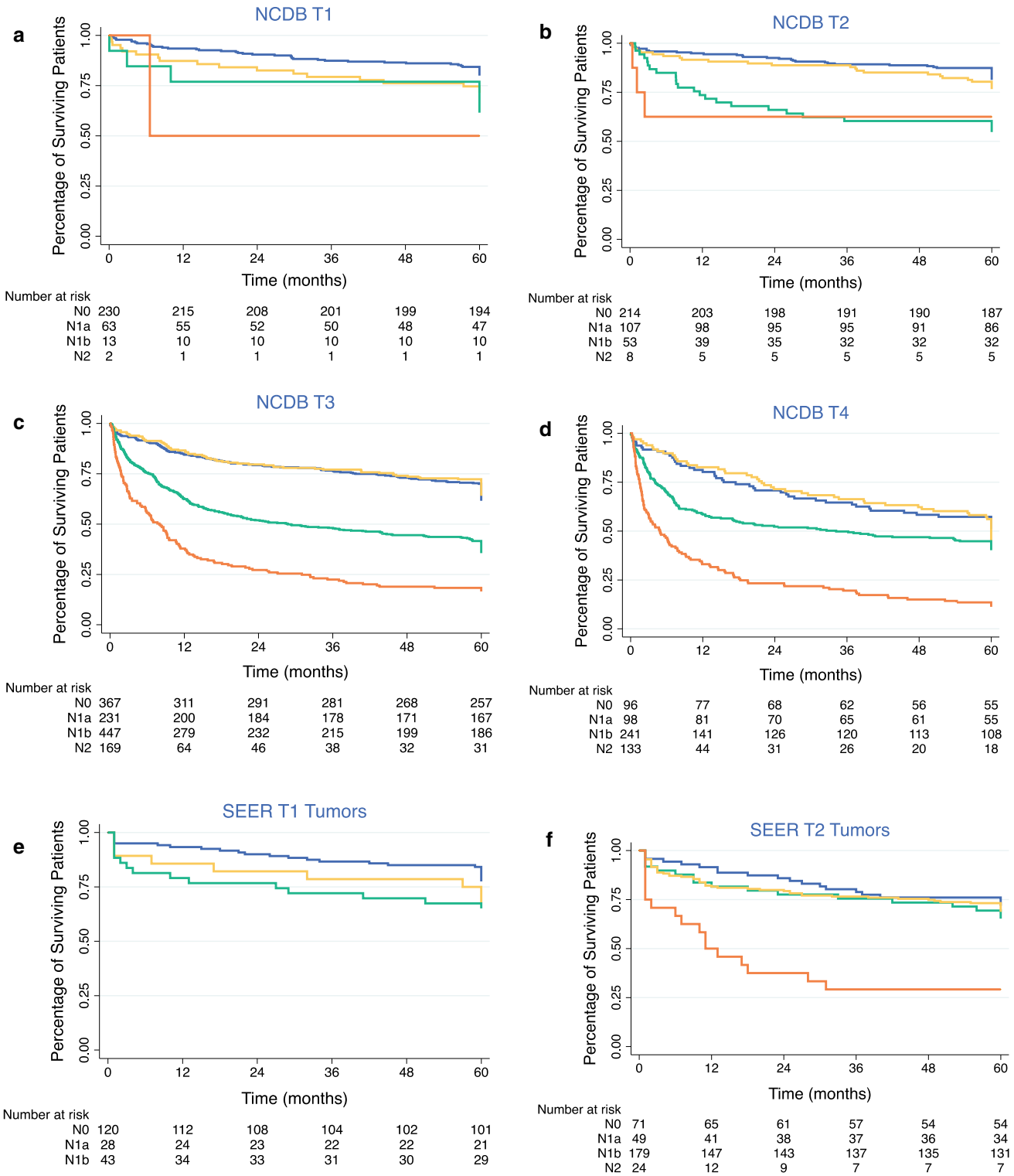

FIG. 2 Kaplan–Meier survival curves for new N classification stratified by T-stage in NCDB and SEER

because T1 tumors have low rates of lymph node metastasis. Colon NET patients with a higher AJCC T stage, signifying a larger tumor or a greater depth of invasion, may have increased spread to regional lymph nodes and may require more extensive resection.

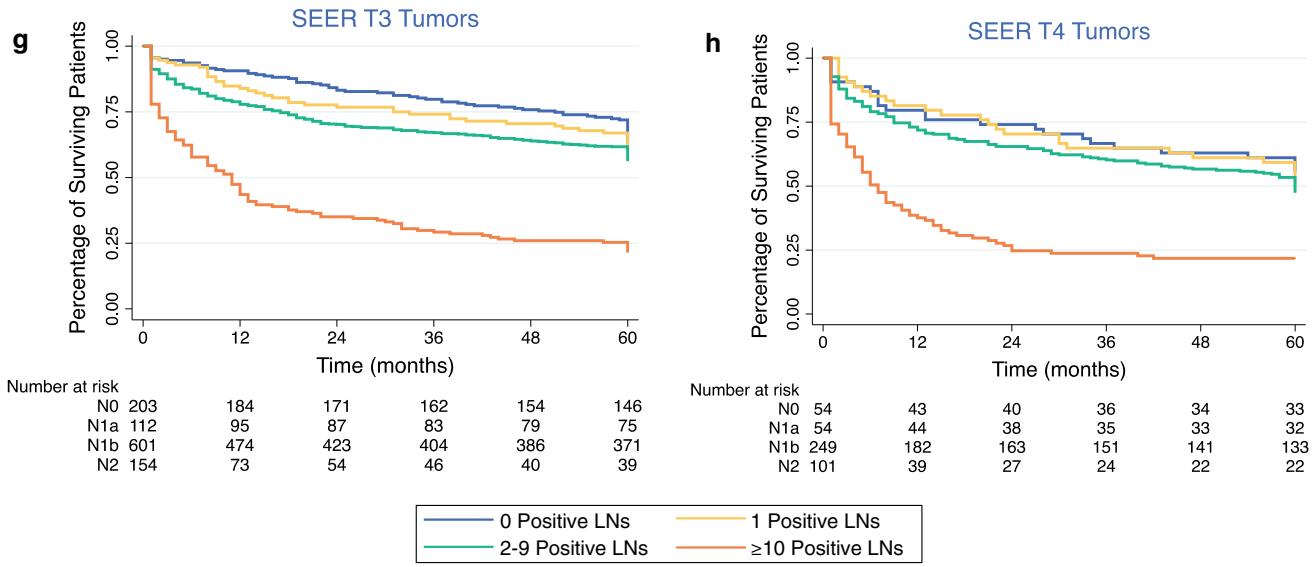

FIG. 2 continued

TABLE 3 Univariable and multivariable analysis of overall survival in NCDB

	Univariable			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.04	1.03–1.04	< 0.001	1.03	1.03–1.04	< 0.001
Sex (ref: Male)	0.88	0.78–0.98	0.02	0.91	0.81–1.03	0.13
Race (ref: white)						
Black	0.76	0.63–0.92	0.04	0.99	0.81–1.21	0.93
Other	0.93	0.66–1.29	0.65	1.01	0.72–1.44	0.93
Charlson/Deyo score (ref: 1)						
2	2.08	1.72–2.52	< 0.001	1.66	1.36–2.03	0.001
Tumor differentiation (ref: well/moderate)						
Poor/undifferentiated	5.99	5.04–7.14	< 0.001	3.91	3.25–4.70	0.001
AJCC T classification (ref: T1)						
T2	1.07	0.78–1.46	0.67	0.83	0.60–1.14	0.24
T3	3.02	2.36–3.86	0.001	1.21	0.93–1.57	0.16
T4	4.10	3.17–5.30	0.001	1.35	1.02–1.79	0.04
AJCC N classification (ref: N0)						
N1	2.51	2.20–2.88	0.001	–	–	–
Proposed N classification (ref: N0)						
N1a	1.23	1.02–1.49	0.001	1.24	1.02–1.50	0.03
N1b	2.77	2.39–3.22	0.001	2.83	2.40–3.34	0.001
N2	6.01	5.06–7.13	0.001	4.70	3.88–5.69	0.001
No of positive LNs	1.05	1.04–1.05	0.001	–	–	–
Lymphovascular Invasion present	2.85	2.25–3.61	0.001	1.05	1.04–1.07	0.001
Positive margin	2.10	1.83–2.41	0.001	1.40	1.21–1.61	0.001

NCDB Nataional Cancer Database, *HR* hazard ratio, *CI* confidence interval, *ref* reference value, *AJCC* American Joint Committee on Cancer, *LN* lymph node

Given our data indicating that the total number of positive lymph nodes influences survival, guidelines surrounding adequate lymphadenectomy should be reviewed. Currently, no consensus guideline exists for a minimal sampling number of lymph nodes by the National Comprehensive Cancer Network, NANETS, or ENETS.

This likely is due to the previous unknown prognostic data regarding the number of positive lymph nodes in colon NETs. In contrast, for colon adenocarcinoma, a minimum of 12 retrieved lymph nodes is the standard of care.[18] Because the median number of lymph nodes examined in each new nodal staging group was 12 or more, the optimal number of retrieved lymph nodes likely is close to 12. However, additional investigations are warranted to assess the optimal number of retrieved lymph nodes for colon NETs.

The current study had several strengths. First, the study was conducted using a national multicenter database, which allowed for a large sample size and generalizable data. Second, the proposed nodal staging classification was validated by use of a second national cancer database. Third, all patient information is validated with continuous audits, making the data reliable.

Our findings, however, must be viewed within the context of the study design. First, patients were excluded from the study if lymph node data were absent. Moreover, the tumor differentiation variable was not available for all the patients, and this could have influenced overall survival. Second, our new nodal classification was derived from overall patient survival rather than from disease-specific survival. Third, tumor-specific variables related to colon NETs such as Ki-67 level, mitotic level, and morphology as well as data on adjuvant therapy were not obtained because they are not recorded in the database.

In conclusion, for patients with colon NETs, the total number of positive lymph nodes is an independent predictor of survival. Using data from a national cancer database that were subsequently validated, we demonstrated that patients with no positive lymph nodes, 1 positive lymph node, 2–9 positive lymph nodes, and 10 or more positive lymph nodes have distinct survival outcomes. A re-classification of the current binary staging system into N0, N1a, N1b, and N2 for nodal staging of colon NETs will provide patients with more accurate survival outcomes.

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CONFLICT OF INTEREST The authors declare that they have no conflict of interest.

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