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The Role of Alternative Lymph Node Classification Systems in Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NEN): Superiority of a LODDS Scheme Over N Category in Pancreatic NEN (pNEN)

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ABSTRACT

Lymph node (LN) involvement in gastroenteropancreatic neuroendocrine neoplasms (GEP-NEN) has been reported to have prognostic and therapeutic implications. Numerous novel LN classifications exist; however, no comparison of their prognostic performance for GEP-NEN has been done yet. Using a nationwide cohort from the German Neuroendocrine Tumor (NET) Registry, the prognostic and discriminatory power of different LN ratio (LNR) and log odds of metastatic LN (LODDS) classifications were investigated using multivariate Cox regression and C-statistics in 671 patients with resected GEP-NEN. An increase in positive LN (pLN), LNR, and LODDS was associated with advanced tumor stages, distant metastases, and hormonal functionality. However, none of the alternative LN

classifications studied showed discriminatory superiority in predicting prognosis over the currently used N category. Interestingly, in a subgroup analysis, one LODDS classification was identified that might be most appropriate for patients with pancreatic NEN (pNEN). On this basis, a nomogram was constructed to estimate the prognosis of pNEN patients after surgery. In conclusion, a more accurate classification of LN status may allow a more precise prediction of overall survival and provide the basis for individualized strategies for postoperative treatment and surveillance especially for patients with pNEN.

Introduction

Neuroendocrine neoplasms (NEN) represent a rare, highly heterogeneous group of malignancies of neuroendocrine origin, most commonly arising in the gastroenteropancreatic (GEP) or bronchopulmonary endocrine system [1]. Approximately 70 % of cases are GEP-NEN, with the pancreas (pNEN) and small intestine (siNEN) being the most common primary tumor sites [2, 3]. Historically, GEP-NEN have been stratified into foregut, midgut, and hindgut according to their site of origin in the embryonic gut. Interestingly, a marked increase in the incidence of GEP-NEN has been observed in recent decades, which is especially attributed to improved diagnostic procedures [3, 4]. According to the current WHO classification, GEP-NEN are divided based on their histological differentiation and Ki67 proliferation index or the mitotic count into well differentiated neuroendocrine tumors (NET G1/G2/G3) and poorly differentiated large cell or small cell type neuroendocrine carcinomas (NEC G3), or into mixed neuroendocrine/non-neuroendocrine neoplasms (MiNEN) [5–7]. The prognosis of GEP-NEN is known to be highly variable [8]. Therefore, precise tumor classification and optimal risk stratification are essential for adequate treatment. Diagnostic and therapeutic decision-making principles are based on such characteristic features of GEP-NEN as proliferative activity, somatostatin receptor (SSTR) expression, tumor growth rate, tumor localization, and tumor extent. To date, staging of GEP-NEN has been based on the Tumor Node Metastasis (TNM) classification of the 8th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) [9, 10], and lymph node involvement in GEP-NEN has been reported to have significant prognostic impact and therapeutic implications [11–13]. However, lymph node staging of NEN is not uniform for all NEN according to the TNM classification. For well differentiated NET, lymph node staging is currently performed according to the TNM classification into N0 and N1, considering only the presence or absence of regional lymph node involvement. An exception is well-differentiated siNET of the jejunum and ileum, where lymph node metastasis is differentiated into N1 (number of positive lymph nodes < 12) and N2 (number of positive lymph nodes greater than or equal to 12 or lymph node conglomerates in the mesentery larger than 2 cm) [9, 10]. In contrast, NEC are classified according to the criteria of the classifications for carcinomas of the respective localization. However, no consideration is given to the extent of total lymph node involvement or surgical radicality in lymphadenectomy. Consequently, alternative lymph node classification systems such as lymph node ratio (LNR), defined as the number of positive lymph nodes (pLN) divided by the total number of lymph nodes dissected, and log odds of positive lymph nodes (LODDS), defined as the logarithm of the ratio between the probability of being a positive node and the probability of being a negative node when a lymph node is harvested, have been developed. Although these alternative lymph node classifications have provided improved prognostic stratification in tumors such as colorectal cancer [14], pancreatic cancer [15], and medullary thyroid cancer [16], their prognostic impact specifically for GEP-NEN has not been well studied to date. Recently, Jiang et al. investigated the prognostic capability of different lymph node classification schemes in 3680 patients specifically with small intestine neuroendocrine tumor (siNET) based on the Surveillance, Epidemiology, and End Results (SEER) database [17]. The authors concluded that for prognostic evaluation of siNET, LODDS and LNR were more useful and informative than the number of pLN [17]. Given the lack of comparable data so far, the aim of this study was to evaluate and compare the different alternative lymph node classification systems for GEP-NEN in terms of their prognostic impact using real-world data from a nationwide cohort from the German Neuroendocrine Tumor (NET) Registry.

Materials and Methods

Patients and procedures

All data in this study were obtained from the German NET Registry, which is a multicenter and multidisciplinary project from Germany founded in 2004 and organized by the Working Group on Endocrine and Neuroendocrine Oncology (formerly AG-NET) of the German Society of Endocrinology. Prior to documentation of patient data, signed informed consent was collected from each of the participating centers from NEN patients eligible for recruitment.

Data were documented retrospectively for the period between 1999 and 2004 and prospectively thereafter to the present and transferred to an MS Access database (Lohmann & Birkner Health Care Consulting, GmbH, Berlin, Germany). Specific inclusion criteria of our study were an age at the time of enrollment in the German NET Registry of at least 18 years and histologically confirmed GEP-NEN G1, G2, and G3, defined as NEN with a Ki67 labeling index ≤ 2 %, 3 % to 20 %, and > 20 %, or documented NEC according to the 2010, 2017, or 2019 WHO classification. Specific exclusion criteria comprised incomplete TNM, no grading, unclear/missing lymph node numbers, undefined localization, non-GEP, missing survival data/lost to follow-up, no surgery for primary, mixed histologies (mixed adenoneuroendocrine carcinoma/MANEC; mixed neuroendocrine/non-neuroendocrine neoplasms/MiNEN), death within the first 30 postoperative days. The initial patient cohort consisted of 2838 patients, of whom 671 patients were finally included in the analyses after review of the inclusion and exclusion criteria (**Fig. 1S**).

The collected data included personal information such as sex, age, date of initial diagnosis, last visit or date of death. In our survival analyses, we used overall survival (OS) as the primary endpoint, which we defined as the time interval between initial diagnosis and death from any cause or last call. In addition, disease-specific information such as tumor manifestation at initial diagnosis, localization of primary tumor, presence or absence of metastases, date of discovery of metastases, localization of metastases, presence or absence of functionality, available histopathologic classification criteria (NET or NEC and Ki67 labeling index), and staging information was obtained. In cases where more than one histologic report was available, the highest documented Ki67 labeling index was used for further analyses. Finally, treatment-specific information was recorded with respect to overall outcomes.

Tumor staging and lymph node classification

All tumors were reclassified based on the available histopathologic data and lymph node counts according to the 8th edition of the AJCC/UICC [9, 10]. LNR was defined as the number of positive lymph nodes divided by the number of lymph nodes examined (NELN). LODDS was calculated using the following formula: log[(number of pLN + 0.5)/(NELN – number of pLN + 0.5)]. The novel lymph node classification schemes were analyzed as both continuous and categorical variables. For the categorical variables, we used cut-off values and resulting subcategories proposed by 26 different studies for LNR [18–43] and 28 different studies for LODDS [20–23, 25–29, 31, 35, 38–40, 42–55]. Proposed cut-off values published after January 19, 2021, were not included in our analysis.

Statistical analysis

Scatter plots were created, and Spearman's correlation coefficient was calculated to examine the relationship between the number of pLN, LNR and LODDS. Then, the area under the receiver operating characteristic (ROC) curve (AUC) was calculated to evaluate the accuracy of pLN, LNR and LODDS as continuous variables. While an AUC of 1 represents the best prediction, an AUC value greater than 0.7 indicates a good model and 0.5 indicates that the prediction is no better than chance. The statistical significance of the differences between the individual AUCs was tested using the DeLong test [56]. Kaplan–Meier curves were plotted and then compared with the log-rank method. The prognostic potential of the lymph node classifications studied, when used as categorical variables, was examined by a multivariate Cox regression analysis. Therefore, a base model included the following covariates: Patient age (< median versus ≥ median) and sex (female versus male), tumor localization (foregut versus midgut or hindgut), extent of tumor (T3 + 4 versus T1 + 2), grading (G1 versus G2 or G3), and presence of metastatic disease (M0 versus M1). Applying this multivariate base model, we estimated hazard ratios (HR) for each lymph node classification and assessed model discrimination using C-statistics, as described recently [14–16]. Briefly, for each model, the difference between the C-index of the model containing the N category and any other model with an alternative lymph node classification was compared. This difference was quantified by calculating delta C (defined as C difference from N category), and FDR (False discovery rate)-adjusted p-values (Pc). Values of the C-index and thus the precision of the model prediction are interpreted in the same manner as the AUC (1 = perfect model; > 0.7 = good model; < 0.5 very poor model). Different subgroups of the patient population were further analyzed as described above. Finally, we created a nomogram from the best model. Internally, the reproducibility of our nomogram was validated using the bootstrap resampling (B = 100) and assessing the calibration curve.

Statistical analyses and graphical representations were performed using either GraphPad Prism for Windows (version 5; GraphPad Software Inc., La Jolla, CA, USA) or the R software package (version R4.1.1, R Foundation for statistical computing) [57]. Reporting tools based on the R package "knitr" were used, as well as the R packages "readxl", "survival", "survminer", "labelled", "naniar", "broom", "glue", "gghighlight", "janitor", "gtsummary", "tidyverse", "pROC", "ggplot2" and "rms" [58–72].

Results

Patients with histologically confirmed GEP-NEN whose initial diagnosis was made between 9/1998 and 12/2020 were included in the study. The baseline clinicopathologic characteristics of the patients are detailed in ▶ **Table 1**. With defined inclusion and exclusion criteria (**Fig. 1S**), a total of 671 patients with GEP-NEN were finally enrolled in this study. The median NELN was 15 (range: 1–68) and the median of pLN was 2 (range: 0–35).

We first investigated whether LNR or LODDS were associated with clinicopathologic variables in patients with GEP-NEN. Advanced tumor extent (T3 + 4), distant metastasis at the time of surgery as well as hormonal functionality were associated with increases in all pLN, LNR and LODDS (▶ **Fig. 1**). In addition, a higher number of pLN, as well as increased LNR and LODDS, were found in G2 tumors compared with G1 tumors. Higher numbers of pLNs and an increasing LNR were also detected more frequently in midgut and hindgut tumors. For LODDS, however, we observed this only in midgut tumors. While LODDS was associated with patient age, we did not observe this for the number of pLN and LNR. However, we were unable to demonstrate any differences between female and male patients.

Subsequently, ROC curves for LODDS, LNR and pLN were constructed as continuous variables to predict 1-, 3-, and 5-year OS (▶ **Fig. 2a–c**). Thereby, the number of pLN showed a significantly better prediction for 1- and 3-year OS (AUC: 0.774 and 0.632) compared with the LNR (AUC: 0.724 and 0.584; p-value: 0.04 and 0.01) and LODDS (AUC: 0.725 and 0.572; p-value: 0.05 and 0.01), respectively. However, there were no significant differences in predictive quality for 5-year OS (AUC_{pLN}: 0.624; AUC_{LNR}: 0.636; AUC_{LODDS}: 0.626).

In order to investigate the relationship between pLN, LNR and LODDS, we created scatter plots and calculated the correlation coefficient (▶ **Fig. 3a–c**). Accordingly, both alternative lymph node classifications showed increasing values in parallel with the number of pLN (LODDS: $r_s = 0.790$, LNR: $r_s = 0.647$). In addition, we found a high correlation between LODDS and LNR ($r_s = 0.859$).

In an attempt to make the LNR and LODDS more clinically applicable, different categories of these continuous variables have been defined over the past decades by various research groups using numerous statistical categorization methods. We first con-

▶ **Table 1** Patient characteristics.

Variables	All patients (%)
Number of subjects	671
Age	
Median (range)	59 (19–87)
Gender	
Male	339 (50.52)
Female	332 (49.48)
Localization (organ)	
Esophagus	1 (0.15)
Stomach	20 (2.98)
Duodenum	31 (4.62)
Small intestine	362 (53.95)
Pancreas	179 (26.68)
Appendix	25 (3.73)
Colon	53 (7.9)
Extent of tumor (T)	
T1	92 (13.71)
T2	168 (25.04)
T3	299 (44.56)
T4	112 (16.69)
Lymph node metastasis (N)	
N0	180 (26.83)
N1	447 (66.62)
N2	42 (6.26)
N3	2 (0.3)
NELN median (range)	15 (1–68)
pLN median (range)	2 (0–35)
Distant metastasis (M)	
M0	270 (40.24)
M1	401 (59.76)
Resection margin (R)	
R0	446 (66.47)
R1	85 (12.67)
Missing	140 (20.86)
Differentiation (G)	
G1	358 (53.3)
G2	262 (39.1)
G3	51 (7.6)
Functionality	
Yes	418 (62.3)
No	113 (16.84)
Missing	140 (20.86)

LN: Lymph node; NELN: Number of examined LNs; pLNs: Positive LNs.

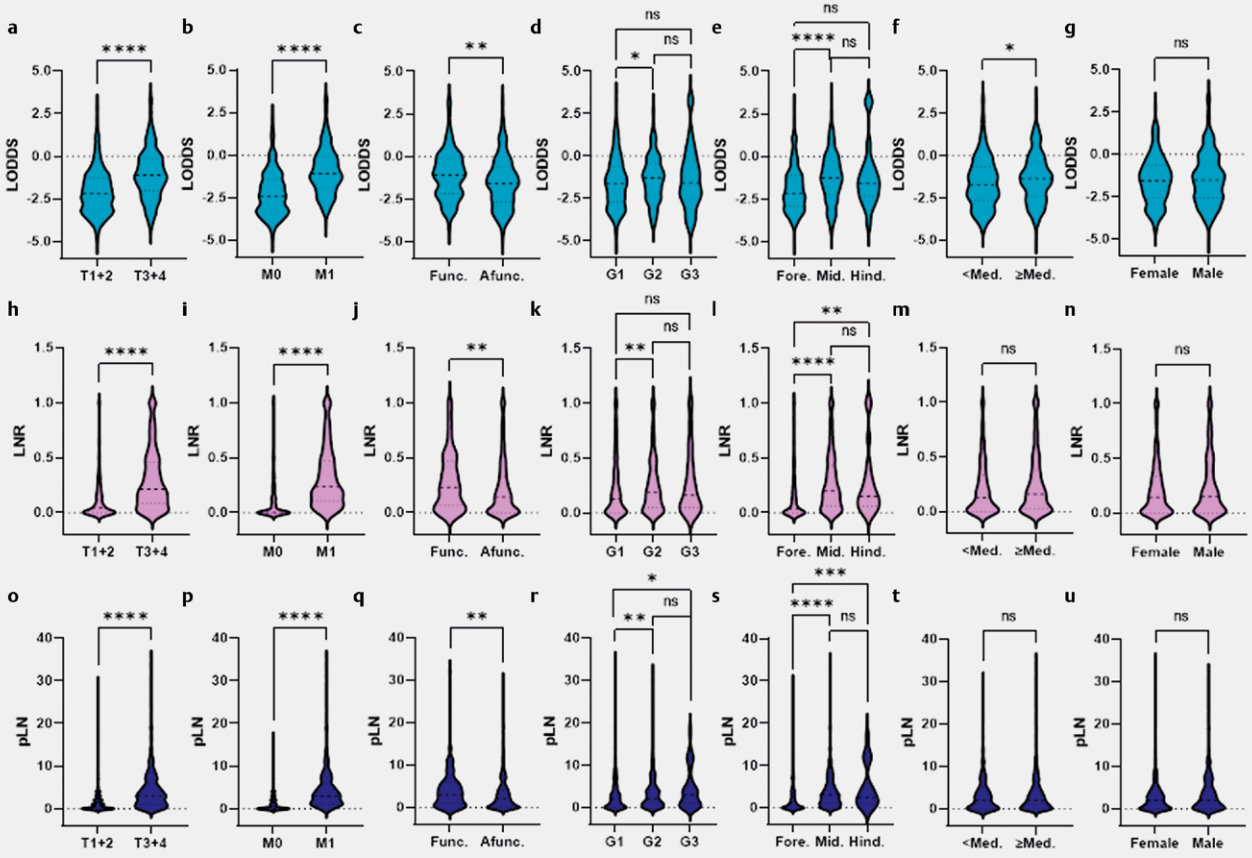
structed Kaplan–Meier survival curves that reflected a significant ($p < 0.05$) association with OS for each alternative lymph node classification system published to date as well as for the classical N category (**Fig. 2S–6S**). To investigate any superiority of the different LNR or LODDS classifications over the commonly applied N category, we performed a Cox proportional hazards regression analysis followed by an assessment of model discrimination for each lymph node classification system using C-statistics. To this end, we first constructed a base model of the variables sex, age, localization, tumor extent, distant metastasis, and grading and determined their prognostic value in the overall population using Cox regression analysis. Accordingly, the patient age at the time of initial diagnosis, the localization in the hindgut, and also the grading were prognostically independent factors (▶ **Table 2**).

Using this base model, we next performed multivariate Cox regression analysis for each lymph node classification system separately (**Tables 1S and 2S**), and then assessed model discrimination by C-statistics (**Tables 3S and 4S**). Interestingly, none of the alternative LNR or LODDS classifications was found to be superior to the classic N category (N0: HR 1 [reference]; N1: HR 1.412, CI 0.623–3.200; N2: HR 2.978, CI 1.095–8.099; N3: 12.206, CI 1.281–116.332), which displayed a C-index of 0.736 ($C_{SE} = 0.036$), in terms of prognostic predictive power.

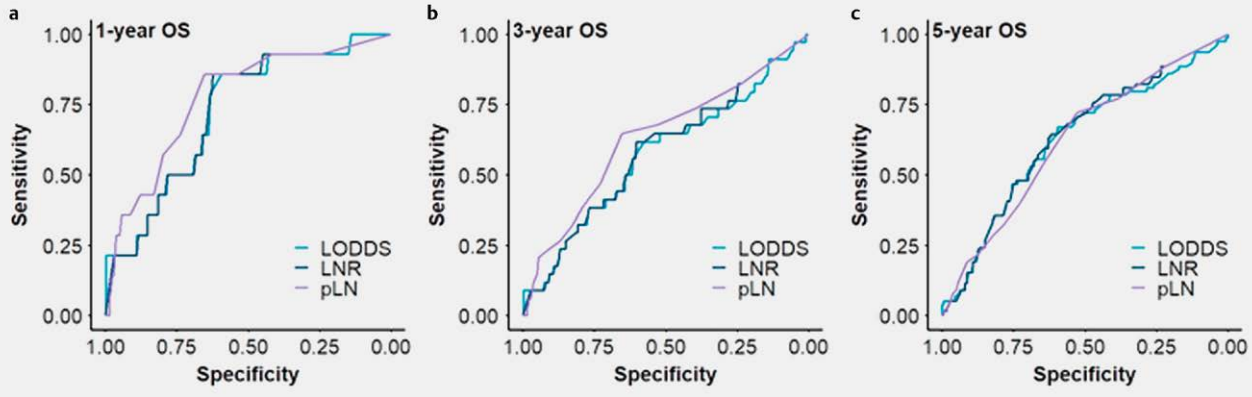
Based on this result, we were wondering whether there is a special subgroup of patients with GEP-NEN in whom an alternative lymph node classification might nevertheless be preferable to the N category. However, because we could not include a sufficient number of patients for each variable that would allow us to obtain reliable results, we reiterated the Cox regression analysis and C-statistics that we performed for the entire cohort in the subgroups of patients with or without distant metastases (M0 and M1), NEN G1 or G2, and pNEN or siNEN. Importantly, a classification system is only of practical and clinical relevance if its subcategories have gradually increased HRs, implying a decreased probability in OS for the higher subcategories. In addition, the subcategories of the ideal lymph node classification system should all display statistical significance. Note that **Tables 5S** and **6S** summarize the results of this analysis. Only the LODDS classification proposed by Persiani and co-workers [48] fulfilled the requirement as the only alternative lymph node classification, such as statistically significant, gradually increasing HRs (LODDS1: HR 1 [reference]; LODDS2: HR 3.736, CI 0.793–17.601; LODDS3: HR 6.037, CI 1.782–20.456) and at the same time a significantly ($p = 0.024$) better discriminative power (C-index: 0.848; C_{SE} 0.044) compared with the N category (C-index: 0.784; C_{SE} 0.058), but only in the group of patients with pNEN. For the other subgroups, however, there was no predictive advantage of the alternative lymph node classifications over the classic N category.

Finally, using multivariate Cox regression analysis, we constructed a nomogram based on our base model and the best-performing lymph node classification model (LODDS classification by Persiani et al. [48]) in the subgroup of pNEN (▶ **Fig. 4a**).

According to this nomogram, a male (13 points), 60-year-old patient (14 points) without distant metastases (M0; 7 points) and G3 (100 points) pNEN at T3 stage with LODDS category 3 (99 points), according to Persiani et al. [48], achieves a total score of 233 points, corresponding to 1-, 3-, and 5-year OS probabilities of



▶ **Fig. 1** Association between LN parameters and clinicopathologic variables: Violin plots depicting the association of LODDS (**a**–**g**), LNR (**h**–**n**), and pLN (**o**–**u**) with T category (**a**, **h**, and **o**) (Extent of tumor; T1 + 2; T3 + 4); presence of distant metastasis (M0 or M1) (**b**, **i**, and **p**); hormonal functionality (functional or afunctional) (**c**, **j**, and **q**); grading (G1, G2 , or G3) (**d**, **k**, and **r**); localization (foregut, midgut or hindgut) (**e**, **l**, and **s**); age (< median or ≥ median) (**f**, **m**, and **t**); and sex (female or male) (**g**, **n**, and **u**). ** $p < 0.01$; **** $p < 0.0001$.

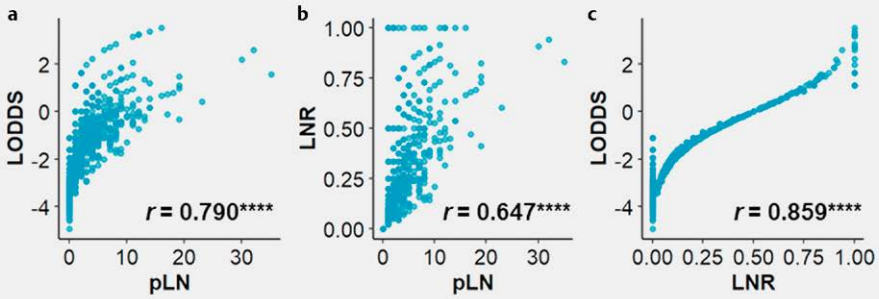


▶ **Fig. 2** ROC analysis of the different lymph node classification systems: ROC curves were generated for LODDS, LNR, and pLN as continuous variables to predict (**a**) 1-year, (**b**) 3-year and (**c**) 5-year OS.

approximately 90, 68, and 59 %, respectively. Internal validation of our model by bootstrap resampling revealed a parallel progression of the curve to the diagonal ideal line, highlighting a strong agreement between predicted and observed events (▶ **Fig. 4b**).

Discussion

Precise staging and prognostic assessment are essential for adequate treatment of GEP-NEN. Lymph node involvement in GEP-NEN



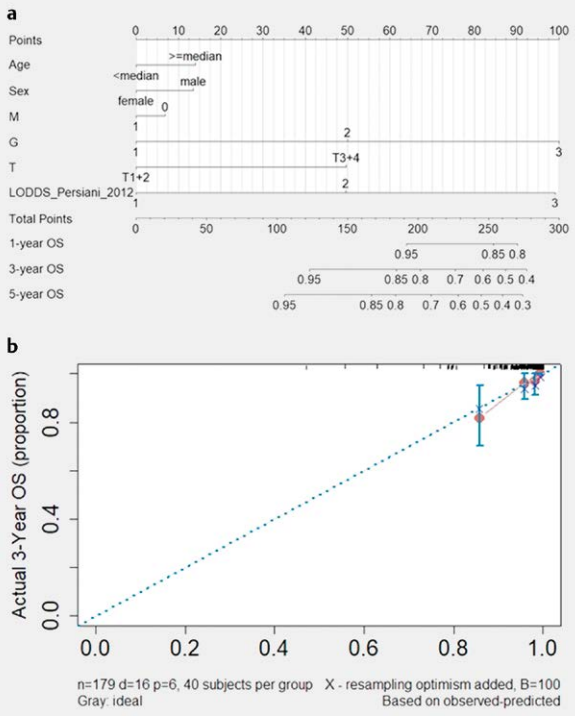
▶ **Fig. 3** Relationship between pLN, LNR and LODDS: Scatter plots presenting the distribution of LODDS versus pLN (**a**), LNR versus pLN (**b**), and LODDS versus LNR (**c**). **** p<0.0001.

▶ **Table 2** Cox regression analysis of the variables included in the multivariate adjusted base model.

Clinicopathological variables	HR (95% CI)	p-value
Sex		
Female	1.00 (reference)	
Male	1.29 (0.81–2.04)	0.283
Age		
<Median	1.00 (reference)	
≥Median	1.68 (1.05–2.68)	0.031
Localization		
Foregut	1.00 (reference)	
Midgut	1.16 (0.66–2.02)	0.613
Hindgut	2.84 (1.17–6.87)	0.020
Extent of tumor		
T3+4	1.00 (reference)	
T1+2	0.68 (0.39–1.19)	0.176
Distant metastasis		
M0	1.00 (reference)	0.102
M1	1.62 (0.91–2.89)	
Grading		
G1	1.00 (reference)	
G2	2.00 (1.19–3.36)	0.009
G3	7.15 (3.54–14.44)	<0.0001

has been reported to have significant prognostic value and therapeutic implications [11, 12], but its classification has not been performed uniformly for all GEP-NEN. Therefore, the present study used population-based data from the German NET Registry and evaluated the relative discriminatory power of different lymph node staging systems to predict survival of patients with GEP-NEN. The currently most common lymph node staging depends only on the presence or number of pLN, not taking into account the NELN or negative lymph nodes. Accordingly, if the number of pLN is the same, patients with an insufficient low NELN might have a worse prognosis. Such understaging is referred to as staging migration or the Will Rogers phenomenon [73]. Consequently, novel lymph node classification schemes have been developed in recent years in an attempt to more accurately stratify cases into alternative patient subgroups. The LNR was initially introduced as a scheme that considers not only the number of pLN but also the extent of lymphadenectomy. However, with this classification, there is no possibility to further stratify cases with LNR values of 0 or 1. Therefore, LODDS was established as another classification that accounts for the extent of surgical radicality in lymphadenectomy and subdivides cases that have either no tumor infiltration of the removed lymph nodes or infiltration of all removed lymph nodes. Since both LNR and LODDS represent continuous variables and as such have limited clinical relevance, various subcategories with different cut-off values have been analyzed in different studies to express the advanced stage of tumor disease and ideally also to have prognostic significance. To date, however, there are only few studies that have examined the prognostic capability of alternative lymph node classifications specifically for GEP-NEN. To our knowledge, our study was the first to compare several alternative lymph node classification systems defining different cut-off values in patients with GEP-NEN in terms of their prognostic impact.

We would also like to emphasize that we intentionally included patients in our study who had only a small number of lymph nodes examined, as it is in these patients that the alternative lymph node classifications may be beneficial for prognostic assessment. In this context, Guarneri et al. [74] and Partelli et al. [75] recently demonstrated that a minimum of 12 and 13 lymph nodes should be examined in pNEN after distal pancreatectomy and pancreaticoduodenectomy, respectively, for adequate staging. Therefore, in our analysis, we also performed a subgroup analysis according to the extent of lymphadenectomy (data not shown). However, in the patient groups in which either less than 12 lymph nodes (n = 227) or at least 12 lymph nodes (n = 444) were removed, there was no prognostic advantage of an alternative lymph node classification over the N category. Interestingly, it has been shown that lymph node staging according to LODDS appears to be particularly beneficial in patients with inadequate lymphadenectomy [49]. So far, for pNEN, 8th edition of the AJCC/UICC based on the number of pLN is the most widely accepted system for nodal staging [9, 10]. In a retrospective study by Gao et al., 2295 patients with pNEN were eval-



▶ **Fig. 4** Nomogram for predicting the probability of patient survival: **(a)**: A nomogram composed of the independent variables age, sex, presence of distant metastases (M0 or M1), grading (G1, G2, or G3), extent of tumor (T1 + 2 or T3 + 4) and LODDS according to Persiani et al. [48] predicting 1-, 3-, and 5-year OS. **(b)**: The final model was validated by bootstrap resampling (B = 100 times) based on our data set and calibration curve assessment.

uated for the most effective lymph node staging system for predicting cause-specific survival based on the SEER (Surveillance, Epidemiology, and End Results) database in which the number of pLN, LNR, and LODDS were grouped into 2 and 3 categories, respectively, based on survival curve-defined cut-off values [76]. For the 3-category staging scheme, only the authors' pLN subcategories, which interestingly corresponded to the AJCC/UICC N category subcategories for pancreatic cancer (8th edition), turned out to be an independent prognostic factor. Likewise, for the 2-category staging scheme, in which the pLN subcategories were divided analogously to the AJCC/UICC N category for well differentiated NET (8th edition), only the pLN category proved to be an independent prognostic factor. In addition, the authors; pLN 2- and 3-category schemes had a higher C-index, so the authors concluded that these categorizations had better discriminatory ability than the LNR and LODDS schemes. At this point, however, it should be pointed out that, in contrast to our study, the authors examined only 2 different LNR and LODDS classifications, respectively, did not precisely define the covariates of the multivariate analysis, and did not calculate or report a statistical significance level for the difference of the respective C-indices. Apart from this, Gao and co-workers, in contrast to us, also included MANEC in their study [76]. Another retrospective study published by Gaitanidis et al. examined the prognostic significance of staging models constructed based on LNR cut-off values and compared them with the AJCC 8th edition staging system specifically for pNET, including 896 patients also based on the SEER database [77]. The data demonstrated that a staging model based on LNR ≥ 0.5 was superior to the current AJCC 8th edition staging system. Furthermore, the authors demonstrated that T stage, N stage, distant metastases, degree of differentiation, extent of resection, sex, and age ≥ 57 years were significantly associated with worse disease-specific survival (DSS). In this context, it is worth mentioning that our study stands out compared to previous studies in that, building on our base model and the lymph node classification scheme, which proved to be the most appropriate, we additionally developed a unique nomogram that could be practically very useful for predicting survival probability specifically for patients with pNEN.

Finally, we acknowledge that some limitations should be noted in this study. First, this is a retrospective study design based on a data registry from an independent multicenter cohort, which is subject to inherent bias. The relatively small sample size given the rarity of NEN is another limitation of our work. Third, biochemical parameters of known prognostic relevance, such as chromogranin A (CgA) and SSTR, could not be retrieved for the majority of enrolled patients from the registry and therefore were not included in our study. The fact that we studied only OS and not DFS represents another weakness of the present work. Unfortunately, because the histopathologic evaluation of the tissue samples in the cohort and thus the TNM classification and grading were performed by several pathologists with possibly varying expertise in the field of GEP-NEN based on changing classifications over the past decades, we had to reevaluate older cases using information from the database and thus cannot exclude the possibility that this biased our analysis. Another limitation is that our database does not allow us to provide specific information on the type of preoperative and postoperative staging modalities (e. g., type of imaging) in our patient population. Nevertheless, in this study, we performed a comprehensive analysis of different lymph node classifications with a wide range of cut-off values and obtained new data that could form the basis for future research and be clinically relevant.

Conclusion

This is the first study to compare several novel alternative lymph node classification schemes with a wide variety of cut-off values with the standard N category in patients with GEP-NEN on prognostic impact. Overall, none of the new lymph node classification systems studied showed clear discriminatory superiority in predicting prognosis over the currently used N category in patients with GEP-NEN. However, in a subgroup analysis, LODDS classification as proposed by Persiani et al. [48] was identified as an alternative lymph node classification that might be most appropriate for patients with pNEN. A more accurate classification of lymph node status could more precisely predict OS for these patients and provide the basis for individualized strategies for postoperative treatment and surveillance. Consequently, consideration should be given to incorporating the LODDS classification of Persiani et al. [48] in the risk assessment of patients with pNEN to better stratify their survival and improve their prognosis. Overall, this work should provide an important foundation for future research.

Author Contributions

Conceptualization, S.K., J.T. and A.K.; methodology, S.K., J.T., and A.K.; software, S.K., J.T., D.P., and A.K.; validation, S.K., J.T., S.V., S.H.L., C.R., T.L., W.T.K., and A.K; investigation, S.K., J.T., S.V., D.P., and A.K.; resources, S.K., N.B., S.M., J.T., S.V., D.P., W.T.K, and A.K..; data curation, N.B., S.M.; writing – original draft preparation, S.K., D.P., C.R., and A.K.; writing – review and editing, S.K., J.T., S.V., D.P., S.H.L, C.R., T.L, H.J., R.M., M.S., L.F.G. W.T.K., and A.K.; visualization, S.K., J.T., D.P., and A.K.; supervision, W.T.K., and A.K.; project administration, T.L., W.T.K., and A.K. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board at Charité Mitte, Berlin, Germany, with approval of the updated web-based version on January 31, 2022 (EA1/370/21). In addition, obtainment of local ethics committee approval was mandatory for every participating center.

Informed Consent Statement

Written informed consent for inclusion of their data in the German NET Registry was obtained from all subjects.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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