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The eighth version of American Joint Committee on Cancer nodal classification for high grade pancreatic neuroendocrine tumor should be generalized for the whole population with this disease

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Abstract

Several indexes evaluating the lymph node metastasis of pancreatic neuroendocrine tumor (pNET) have been raised. We aimed to compare the prognostic value of the indexes via the analysis of Surveillance, Epidemiology, and End Results (SEER) database.

We identified pNETs patients from SEER database (2004–2015). The prognostic value of N classification which adopted the 8th American Joint Committee on Cancer (AJCC) N classification for well differentiated pNET, revised N classification (rN) which adopted the AJCC 8th N classification for exocrine pancreatic cancer (EPC) and high grade pNET, lymph node ratio and log odds of positive nodes were analyzed.

A total of 1791 eligible patients in the SEER cohort were included in this study. The indexes N, rN, lymph node ratio, and log odds of positive nodes were all significant independent prognostic factors for the overall survival. Specifically, the rN had the lowest akaike information criterion of 4050.19, the highest likelihood ratio test (χ^2) of 48.87, and the highest C-index of 0.6094. The rN was significantly associated with age, tumor location, tumor differentiation, T classification and M classification ($P < .05$ for all).

The 8th version of AJCC N classification for high grade pNET could be generalized for the pNET population.

Abbreviations: AIC = akaike information criterion, AJCC = American Joint Committee on Cancer, ELN = examined lymph node, EPC = exocrine pancreatic cancer, LNR = lymph node ratio, LODDS = log odds of positive nodes, OS = overall survival, PLN = positive lymph nodes, pNET = pancreatic neuroendocrine tumor, rN = revised N classification, SEER = surveillance, epidemiology, and end results database.

Keywords: lymph node status, pancreatic neuroendocrine tumor, prognosis, surveillance, epidemiology, and end results database

1. Introduction

Pancreatic neuroendocrine tumors (pNETs), originally called pancreatic islet cell carcinomas or pancreatic endocrine tumors, account for about only 3% of pancreatic tumors.[1–3] Partly due to the improved medical technology, it was estimated that the age-adjusted incidence rates increased 6.4-fold between 1973 and 2012 in the US.[1–3]

The accurate evaluation of the lymph node status is quite important for the prognosis prediction and the clinical management. In the 7th version of AJCC staging system for pNET, the N classification was simply defined as N0 [no positive lymph nodes (PLN)] and N1 (at least 1 positive lymph node) for all pNET patients; while in the 8th version launched in January 2018, the N classification of exocrine pancreatic cancer (EPC) and high-grade

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pNET, which excluded the well differentiated pNET, was modified to N0, N1 (1 to 3 PLN) and N2 (≥4 PLN). However, the efficacy of the new tertiary stratification of the N classification for the whole pNET population remained inconclusive.[4–6] Previous studies were limited by the small sample size (usually less than 200) as the incidence of pNETs was relatively low.[7,8] Moreover, the cut-off values of the parameters used in the analyses varied across studies, and most studies included a heterogeneous cohort of patients in terms of baseline characteristics and treatments.[8–10] In addition, alternative lymph node (LN) parameters such as lymph node ratio (LNR)[8,9,11] and log odds of positive nodes (LODDS)[11] have been suggested to substitute the AJCC N classification for better prognostic predictions in certain kinds of solid tumors. Articles evaluating the prognostic value of LODDS in pNET patients have not been published yet. Therefore, studies based on a multicenter database with adequate follow up period might gain more persuading power.

In this context, we performed the present study to compare the prognostic value of N classification which adopted the AJCC 8th N classification for well differentiated pNET, revised N classification (rN) which adopted the AJCC 8th N classification for high grade pNET, LNR and LODDS for patients with resectable pNETs based on the Surveillance, Epidemiology, and End Results (SEER) database.

2. Materials and methods

2.1. Patients and data collection

The SEER database (1973 to 2015) was used to identify pNET patients. The SEER database is publicly available and the data for all patients are de-identified, so the approval and informed consent of the institutional review committee were not required in the current study. Patients were retrieved based on the International Classification of Diseases for Oncology (2nd and 3rd editions) codes for tumors of the pancreas: C25.0 to C25.9. The following International Classification of Diseases for Oncology (3rd edition) diagnosis codes were included: malignant pancreatic endocrine tumor (8150/3), malignant insulinoma (8161/3), malignant glucagonoma (8152/3), malignant gastrinoma (8153/3), malignant mixed pancreatic endocrine and exocrine tumor (8154/3), malignant VIPoma (8155/3), malignant somatostatinoma (8156/3), carcinoid tumor in situ (8240/2), carcinoid tumor NOS (8240/3), enterochromaffin cell tumor (8241/3), malignant enterochromaffin-like cell tumor (8242/3), goblet cell carcinoid (8243/3), mixed adenoneuroendocrine carcinoma (8244/3), neuroendocrine carcinoma in situ (8246/2), neuroendocrine carcinoma NOS (8246/3), and atypical carcinoid tumor (8249/3). The following information was retrieved: age record, race record, sex, year of diagnosis, site recode ICD-O-3/WHO 2008, behavior recode for analysis, primary Site – labeled, grade, diagnostic confirmation, ICD-O-3 Hist/behav, derived AJCC Stage Group 7th ed (2010+), derived AJCC Stage Group 6th ed (2004+), derived AJCC T 7th ed (2010+), derived AJCC N 7th ed (2010 +), derived AJCC M 7th ed (2010+), derived AJCC T, 6th ed (2004+), derived AJCC N, 6th ed (2004+), derived AJCC M, 6th ed (2004+), RX Summ-Surg Prim Site (1998+), CS tumor size (2004+), CS extension 2004, CS lymph nodes 2004, CS metastases at DX 2004, extent of disease (EOD) 10-extent (1988–2003), EOD 10-nodes (1988- 2003), and EOD 10-size (1988–2003), regional nodes examined (1988+), regional nodes positive (1988+), survival months and vital status recode (study cutoff used).

2.2. Inclusion and exclusion criteria

We used the following inclusion and exclusion criteria to filter the cases in our study. Inclusion criteria:

(1) patients diagnosed as pNETs by histologically pathological examination;
(2) patients underwent surgical resection and had at least 1 examined lymph node (ELN);
(3) patients with definite information of the tumor differentiation, tumor size, number of ELN, number of PLN, and tumor metastases;
(4) patients with overall survival longer than a month. Exclusion criteria: the cases with unclear data regarding age, gender, primary site of pancreas, AJCC 6th TNM staging, and survival time.

2.3. Definitions used in our analysis

The N classification was defined as N0 (no PLN) and N1 (≥1 positive lymph node). The revised N (rN) classification was defined as N0 (no PLN), N1 (1–3 PLN), N2 (more than 4 PLN). The LODDS was calculated by log (pnod + 0.5)/(tnod-pnod +0.5)[11] with pnod representing the number of positive nodes and tnod as the total number of examined nodes. And 0.5 was added to both the numerator and the denominator to avoid an infinite number.

The optimal cut-off points of the LNR and LODDS were determined by X-tile plots.[12] In this study, the ratio of cases in the training set vs the validation set was 1:1. X-tile randomly generated the training set and validation set, and both of sets were normalized so that their base survival curves were similar.

2.4. Statistical analysis

Overall survival was analyzed using Kaplan-Meier curves, and log-rank tests were used to evaluate staging systems and other prognostic factors. Multivariate analysis was performed using Cox proportional hazards regression. HRs and 95% CIs were calculated. The prognostic ability of the 4 lymph node status indexes were evaluated by likelihood ratio χ^2 test values, C index and Akaike information criterion (AIC). Higher likelihood ratio χ^2 test values, higher C index and lower AIC were associated with better performance. We also performed a sensitivity analysis by excluding patients with ELN≥15 to rule out the influence of ELN. All statistical analyses were conducted by STATA 12.0 software (STATA, College Station, TX). Statistical significance was defined as a 2-sided $P < .05$.

3. Results

3.1. Patients' baseline characteristics

A total of 1791 eligible patients in the SEER cohort between 2004 and 2014 were included in this study. The baseline characteristics of the patients were presented in Table 1. The median number of ELN was 10 with a range of 1 to 89. And the median number of PLN was 0 with a range of 0 to 47.

Table 1

Clinicopathological features of the patients involved in this study.

Variable	Value
Age (yr)	
≥60	858 (47.9%)[b]
<60	933 (52.1%)[b]
Gender (Male/ Female)	
Male	960 (53.6%)[b]
Female	831 (46.4%)[b]
Tumor location	
Head	547 (30.5%)[b]
Body	251 (14.0%)[b]
Tail	689 (38.5%)[b]
Others	304 (17.0%)[b]
Tumor differentiation	
Well	1337 (74.7%)[b]
Moderate	305 (17%)[b]
Poor	124 (6.9%)[b]
Undifferentiated	25 (1.4%)[b]
Number of examined lymph nodes	10 (1–89)[a]
Number of positive lymph nodes	0 (0–47)[a]
Tumor size (cm)	3 (0.2–99.3)[a]
T classification	
1	610 (33.6%)[b]
2	612 (34.2%)[b]
3	515 (29.2%)[b]
4	54 (3.0%)[b]
N	
0	1147 (64.0%)[b]
1	644 (36.0%)[b]
M classification	
0	1523 (85.0%)[b]
1	268 (15.0%)[b]
TNM	
I	495 (27.6%)[b]
II	557 (31.1%)[b]
III	471 (26.3%)[b]
IV	268 (15.0%)[b]
rN	
0	1147 (64.0%)[b]
1	418 (23.4%)[b]
2	226 (12.6%)[b]
LNR	0 (0–1)[a]
LODDS	−0.98 (−2.08–1.46)[a]

LNR = lymph node ratio, LODDS = Log odds of positive nodes, N = N classification which adopted the AJCC N classification for well differentiated pNET, pNET = pancreatic neuroendocrine tumor, rN = rN classification which adopted the AJCC N classification for high grade pNET, TNM = Tumor-nodal-metastasis.

[a] median (range).

[b] number (percentage).

3.2. The determination of the cut-off values of the indexes

We used the X-tile analysis to explore the cut-off values. We found 0.1 as the best cut-off value for LNR with the maximum Chi-square value of 36.857. No tertile cut-off values were observed for LNR. We also found -0.89 and -0.45 as the best tertile cut-off values for LODDS with the maximum Chi-square value of 32.561.

We also used the X-tile analysis to identify the cut-off value of number of PLN, as the base of N and rN classifications. We found that 1 and 4 were the tertile cut-off values for number of PLN. Coincidently, the tertile cut-off values were the same as the cut-off values defining N0/N1/N2 in the rN.

3.3. The number of ELN and the 4 lymph node status indexes

The patients were categorized according to the number of ELN as: less than 5, 6 to 10, 11 to 15, 16 to 20, 21 to 25, 26 to 30 and more than 30. The distribution of the patients in respective of the 4 indexes within each ELN category was shown in Supplemental Digital Content (table S1, http://links.lww.com/MD/E848) and Figure 1. As ELN increased, the percentage of patients at advanced N classification and rN classification increased faster than that of patients at advanced set of LNR and LODDS (Supplemental Digital Content (table S1, http://links.lww.com/MD/E848) and Fig. 1).

3.4. The prognostic value of N classification, rN, LNR and LODDS

In the univariate analysis, gender, tumor differentiation, T stage, M stage, N, rN, LNR and LODDS were all significant prognostic factors (Table 2, Fig. 2). As N, rN, LNR and LODDS were closely related, only 1 of the 4 factors was included in the multivariate cox regression analysis for each time. In the multivariate analysis, N, rN, LNR and LODDS were all proved to be independent prognostic factors (Table 2).

We further compared the prognostic ability of N, rN, LNR and LODDS in terms of AIC, likelihood ratio test χ^2 and C-index. Among the 4 lymph node status parameters, rN had the lowest AIC of 4050.19, the highest likelihood ratio test (χ^2) of 48.87, and the highest C-index of 0.6094 (Table 3).

In the sensitivity analysis by excluding patients with ELN ≥ 15, LODDS failed to reach statistical significance in the univariate analysis. The sensitivity analysis did not change the results materially (Table 3).

3.5. The clinicopathological factors between patients stratified by rN

In terms of the association between the clinicopathological factors and rN, we observed that rN was significantly associated with age (≥60 vs <60, $P = .03$), tumor location ($P < .001$), tumor differentiation ($P < .001$), T classification ($P < .001$) and M classification ($P < .001$) (Table 4). Particularly, the percentage of patients developed distal metastasis in N2 patients was significantly higher than that of patients in the N1 category (38.5% vs 24.2%, $P < .001$, Table 4).

4. Discussion

The present study, to the best of our knowledge, was the first study systematically comparing the prognostic value of N, rN, LNR and LODDS for patients with pNET via a thorough analysis of the SEER data. The study provided compelling evidence that rN which adopted N classification for high grade pNET had a better prognostic performance than N, LNR and LODDS, suggesting that rN might be recommended for patients with pNET.

According to previous studies, precise classification of the extent of lymph node metastasis offered the ability to predict oncologic hazards and outcomes for an individual patient.[13] In the AJCC 7th staging system, N classification was simply classified as N0 and N1 based on the presence of lymph node metastasis for pNET, which was deficient in its dichotomous

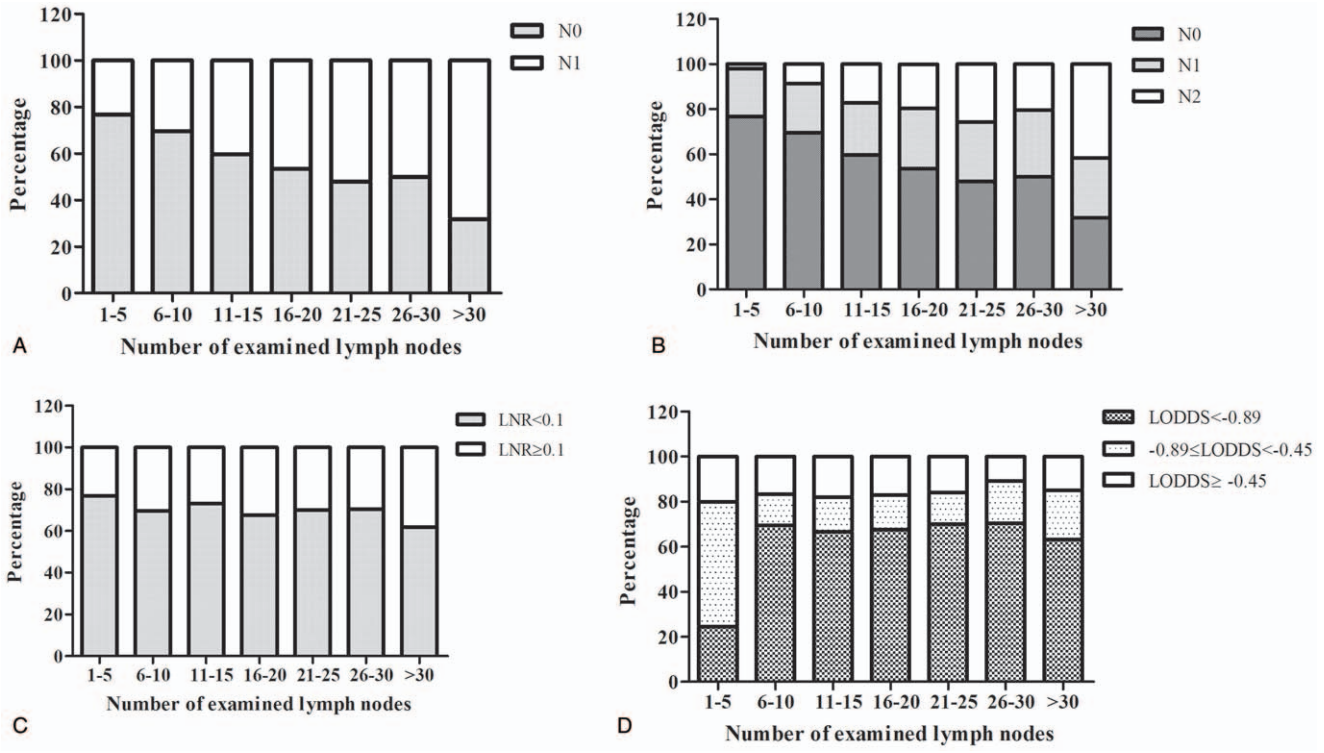

Figure 1. Distribution of patients according to N classification for well differentiated pNET (A), rN classification which adopted the AJCC N classification for high grade pNET (B), lymph node ratio (C) and log odds of positive nodes (D) within examined lymph nodes categories.

Table 2

Univariate and multivariate analysis of the overall survival.

		Univariate analysis	Multivariate analysis		
Variable	**Number**	***P***	**HR**	**95% CI**	***P***
Age (yr)					
≥ 60	858	**<.001**			
< 60	933				
Gender		**.009**			
Male	960				
Female	831				
Tumor differentiation		**<.001**			
Well/ Moderate	1642				
Poor/ Undifferentiated	149				
T classification		**<.001**			
1/2	1213				
3/4	578				
N		**<.001**	**1.478**	**1.157–1.889**	**.002***
0	1147				
1	644				
M classification		**<.001**			
0	1523				
1	268				
TNM		**<.001**			
I/II	1052				
III/IV	739				
rN		**<.001**	**1.345**	**1.156–1.564**	**<.001***
0	1147				
1	418				
2	226				
LNR		**<.001**	**1.465**	**1.148–1.869**	**.002***
≥ 0.10	503				
< 0.10	1288				
LODDS		**<.001**	**1.220**	**1.057–1.409**	**.007***
≥−0.45	316				
−0.89 ~ −0.45	480				
<−0.89	995				

CI = confidence interval, HR = hazard ratio, LNR = lymph node ratio, LODDS = Log odds of positive nodes, N = N classification which adopted the AJCC N classification for well differentiated pNET, pNET = pancreatic neuroendocrine tumor, rN = revised N classification which adopted AJCC N classification for high grade pNET, TNM = Tumor-nodal-metastasis.

* As N, rN, LNR and LODDS were closely related, only 1 of the 4 factors was included in the multivariate cox regression analysis each time.

Significant results were expressed in bold.

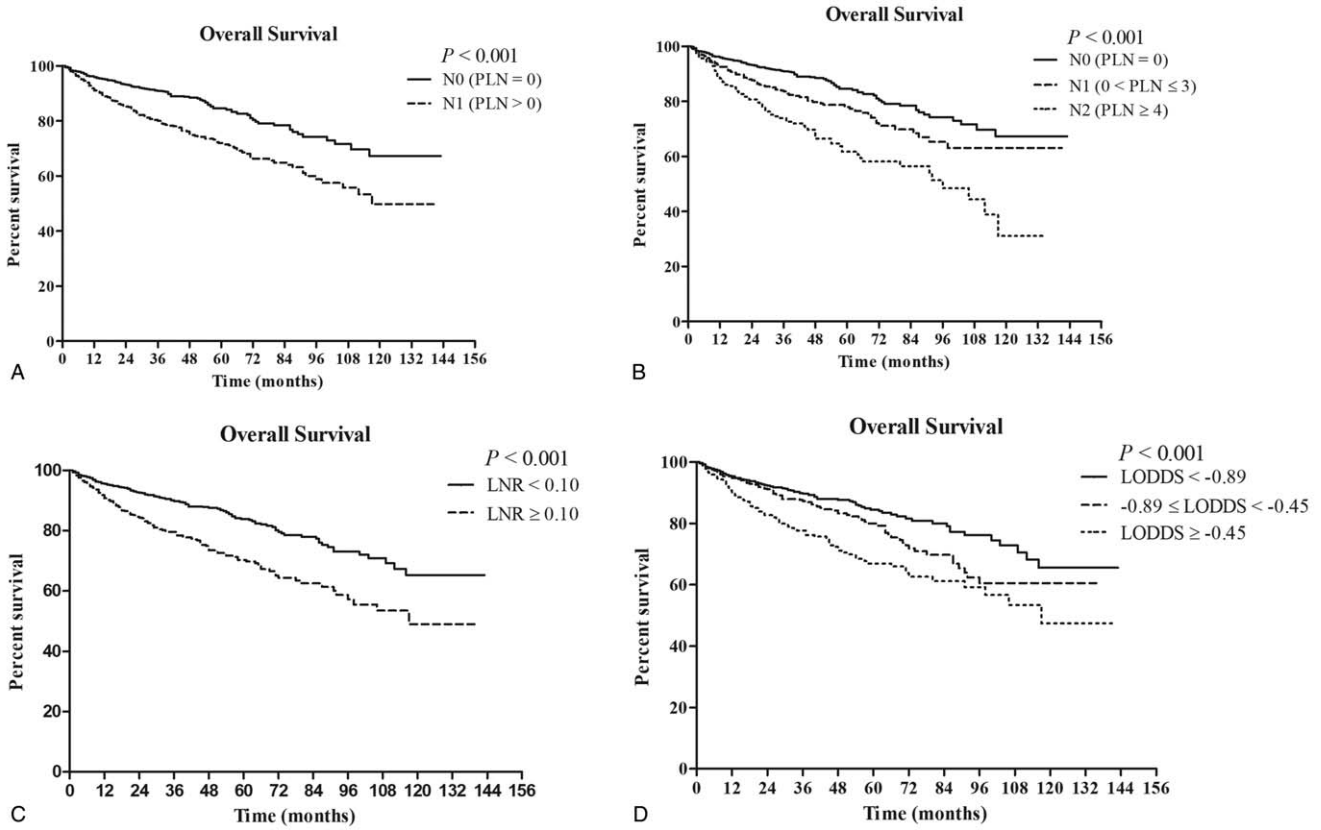

Figure 2. Comparison of the patients' overall survival stratified by N classification for well differentiated pNET (A), rN classification which adopted the AJCC N classification for high grade pNET (B), lymph node ratio (C) and log odds of positive nodes (D).

nature. In the AJCC 8th staging system for high grade pNET and EPC, the definition of N classification was updated. Patients with 1 to 3 PLN were classified as N1 and patients with more than 4 PLN were classified as N2.[4,5,14,15] In the present study, we found that the prognostic value of rN was superior to that of N, which suggested that the N classification for high grade pNET should be applied to the general pNET population.

The results of our study had several clinical implications for the clinicians. Besides providing better discrimination of the survival prognosis, the clinical and the pathological staging of the cancer also serve as a criteria for the design of postoperative management. To our disappointment, there has been no global consensus on the detailed indication of postoperative adjuvant therapies for pNET patients. Our current findings, consistent with prior studies,[13,15] showed that patients with lymph node metastasis indeed had inferior survival outcomes in the perspective of. Adjuvant therapies aiming to prevent the progression of the disease may be indicated specifically in these high-risk patients. The rN might set a basis for future trials to select patients to investigate the role of adjuvant therapies. Further clinical trials based on rN could provide us with more information of the indication, timing, regiment and dosage of the adjuvant therapies. In addition, the results of our study suggested that adequate lymph node dissention, which both render precise staging information and may improve the prognosis, should be further emphasized in the operation.

Unfortunately, there are no exact guidelines for the follow-up of patients with pNET. Based on the current findings, the rN may be utilized in identifying "high risk" subset of the pNET patients who should be followed up much more frequently and carefully. In contrast, cost-effectiveness of follow-up with imaging should be re-evaluated for patients with a lower rN grade in future studies.

Table 3

Comparison of the prognostic performance of N, rN, LNR and LODDS for pNET.

Index	likelihood ratio test χ^2	C-index	AIC
N	36.9	0.5968	4062.159
rN	48.87	0.6094	4050.19
LNR	33.94	0.5884	4065.116
LODDS	29.23	0.5838	4069.83
ELN < 15			
N	19.78	0.5966	2465.439
rN	23.82	0.605	2461.403
LNR	18.12	0.5893	2467.105
LODDS*	–	–	–

AIC = akaike information criterion. Higher likelihood ratio $\chi 2$ test values, C index and lower Akaike information criterion, were associated with better performance, ELN = number of examined lymph nodes, LNR = lymph node ratio, LODDS = log odds of positive nodes, N = N classification which adopted the AJCC N classification for well differentiated pNET, pNET = pancreatic neuroendocrine tumor, rN = revised N classification which adopted AJCC N classification for high grade pNET, TNM = tumor-nodal-metastasis.

* In the subgroup analysis for patients with ELN < 15. LODDS failed to gain statistical significance in the univariate analysis.

Table 4

Comparison of clinicopathological features in patients within rN N0/N1/N2 classifications.

Variable	Value			*P*
	N0 (n = 1147)	N1 (n = 418)	N2 (n = 226)	
Age (yr)				**.033**
≥60	576	183	99	
<60	571	235	127	
Gender (Male/ Female)				.947
Male	612	227	121	
Female	535	191	105	
Tumor location				**<.001**
Head	301	151	95	
Body/Tail	652	197	91	
Others	194	70	40	
Tumor differentiation				**<.001**
Well/Moderate	1094	370	178	
Poor/ Undifferentiated	53	48	48	
T classification				**<.001**
1/2	869	250	94	
3/4	278	168	132	
M classification				**<.001**
0	1067	317	139	
1	80	101	87	

Significant results were expressed in bold. n = number, rN = revised N classification which adopted AJCC N classification for high grade pNET.

The prognostic value of LNR and LODDS were emphasized in recent published articles, as inadequate lymphadenectomy may undermine the clinical efficacy of N stage derived from the absolute number of PLN.[8,11] To the best of our knowledge, our study was also the first study evaluating the prognostic value of LODDS in pNET. In general, stage migration may happen when lymph nodes are examined insufficiently. In order to rule out the influence of number of ELN, we performed a sensitivity analysis by excluding patients with greater than 15 ELN, according to the suggestion by Tol JA et al. in PDAC.[16] The sensitivity analysis did not change the results of the primary analysis materially, which was partly due to the relatively indolent physiological behavior of pNET compared with PDAC.[17] Additionally, it has been suggested that the number of PLN was superior to LNR and LODDS in predicting survival when a high number of LNs were examined.[15,18] The number of PLN increased with increasing numbers of examined LNs, but showed a nonlinear, bimodal trend that is somewhat difficult to explain. LNR decreased constantly with increasing numbers of examined LNs.[19,20]

The current study had several strengths to be noted. First, to the best of our knowledge, the current study was the first to systematically compare the prognostic value of N, rN, LNR and LODDS in patients with pNET. In addition, we conducted thorough data analyses using the multicenter SEER data with a long period of follow-up on patients. Thus our findings might have more implications for the general pNET patients. Meanwhile, there were also some limitations in our study. Firstly, the SEER database did not provide information on certain prognostic factors such as Chromogranin A (CgA), blood vessel invasion, Ki-67 index and mitosis.[21–24] Moreover, information on the endocrine therapy, molecular targeted therapy, chemotherapy and peptide receptor radionuclide therapy was not available.[21–23] Thus, we failed to analyze the implication of the lymph node classification on the selection of the adjuvant therapeutic options, which was of more clinical significance. Secondly, the data regarding another important survival index, the disease free survival, was also not available in the SEER database. Last but not the least, given that the procedure of the surgery was performed according to the location and size of the tumor, we admitted an inevitable heterogeneity could be a limitation of the SEER database. For example, for tumor locating at the pancreatic head, the pancreaticoduodenectomy procedure might be performed; for tumor locating at the tail of pancreas, the distal pancreatectomy might be performed.

5. Conclusion

In conclusion, rN classification was the best nodal staging tool among the N, rN, LNR, and LODDS for the studied pNET patients from the SEER database. Further studies with reasonable study design and adequate follow up are warranted to further strengthen the necessity of modifying the current N classification for pNET.

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Author contributions

Protocol/project development: Mu-xing Li, Chun-hui Yuan, Jian-qiang Cai, Dian-rong Xiu; Data collection or management: Hang-yan Wang, Chao-lai Ma, Bin Jiang; Data analysis: Mu-xing Li, Lei Li; Manuscript writing/editing: Mu-xing Li, Li Zhang, Hong Zhao.

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