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## Retrospective Cohort Study

# Functionality is not an independent prognostic factor for pancreatic neuroendocrine tumors

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## Abstract

### BACKGROUND

Pancreatic neuroendocrine neoplasms (pNENs) that produce hormones leading to symptoms are classified as functional tumors, while others are classified as nonfunctional tumors. The traditional view is that functionality is a factor that affects the prognosis of pNEN patients. However, as the sample sizes of studies have increased, researches in recent years have proposed new viewpoints.

### AIM

To assess whether functionality is an independent factor for predicting the prognosis of pNEN patients.

### METHODS

From January 2004 to December 2016, data of patients who underwent surgery at the primary site for the treatment of pNENs from the Surveillance, Epidemiology, and End Results (SEER) database and West China Hospital database were retrospectively analyzed.

### RESULTS

Contemporaneous data from the two databases were analyzed separately as two cohorts and then merged as the third cohort to create a large sample that was suitable for multivariate analysis. From the SEER database, age ( $P = 0.006$ ) and T stage ( $P < 0.001$ ) were independent risk factors affecting the survival. From the West China Hospital database, independent prognostic factors were age ( $P = 0.034$ ), sex ( $P = 0.032$ ), and grade ( $P = 0.039$ ). The result of the cohort consisting of the combined populations from the two databases showed that race ( $P = 0.015$ ), age ( $P = 0.002$ ), sex ( $P = 0.032$ ) and T stage ( $P < 0.001$ ) were independent prognostic factors. In the West China Hospital database and in the total

Board.

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population, nonfunctional pNETs and other functional pNETs tended to have poorer prognoses than insulinoma. However, functionality was not associated with the survival time of patients with pNETs in the multivariate analysis.

## CONCLUSION

Functionality is not associated with prognosis. Race, age, sex, and T stage are independent factors for predicting the survival of patients with pNETs.

**Key words:** Neuroendocrine tumors; Pancreatic neoplasms; Prognosis; Paraneoplastic endocrine syndromes; Multivariate analysis; Neoplasm staging

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**Core tip:** Pancreatic neuroendocrine tumors (pNETs) are classified into functional and nonfunctional tumors according to the existence of hormones related symptoms or not. The traditional view is that functionality is correlated with the prognosis of pNET patients, which remains a controversial opinion. In this study, we retrospectively analyzed the clinicopathological data of 426 patients from the Surveillance, Epidemiology, and End Results database and 205 patients from the West China Hospital database. The results indicated that functionality is not associated with prognosis. Race, age, sex, and T stage are independent factors for predicting the survival of patients with pNETs.

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## INTRODUCTION

Pancreatic neuroendocrine neoplasms (pNENs) account for approximately 10% of primary pancreatic tumors and the incidence of pNENs has been increasing in recent decades<sup>[1]</sup>. Compared with pancreatic ductal adenocarcinoma, pNENs are generally considered a less aggressive tumor, which occur in relatively younger patients. Neuroendocrine neoplasms (NENs) include a heterogeneous group of neoplasms, and those which produce hormones leading to symptoms (*e.g.*, Whipple triad, Zollinger-Ellison syndrome, and carcinoid syndrome) are classified as functional tumors<sup>[2]</sup>, while others that produce a series of substances without hormone related symptoms are classified as nonfunctional tumors<sup>[2,3]</sup>.

The traditional view is that functionality is a factor that affects the prognosis of pNEN patients. Patients with functional tumors had a longer survival than those with nonfunctional tumors<sup>[4-6]</sup>. Tumors that secrete insulin and cause endogenous hyperinsulinemic hypoglycemia, namely, insulinomas, are believed to have a better prognosis among functional tumors, especially in the early stage<sup>[7]</sup>, while patients with somatostatinoma and vipoma have been reported to have a relatively shorter survival<sup>[8]</sup>.

However, as the sample sizes of studies have increased, researches in recent years have proposed new viewpoints. Due to the lack of specific symptoms, the majority of pNEN cases are diagnosed at a relatively advanced stage<sup>[1]</sup>. Therefore, nonfunctional pNENs are more likely to present with aggressive clinical manifestations<sup>[9,10]</sup>, such as large diameter, increased age, high mitotic count, presence of neural invasion, extrapancreatic organ invasion or metastases, and advanced stage, which may lead to a poor prognosis<sup>[10,11]</sup>. Because of the rarity of pNENs and the low proportion of functional tumors, few studies have performed multivariate Cox regression analysis to show the effect of functionality on survival.

In the present study, we collected data from pNEN patients who underwent surgery at the primary site from the Surveillance, Epidemiology, and End Results (SEER) database and the West China Hospital database. The purpose of this study was to assess whether functionality is an independent factor to predict the prognosis of pNEN patients and explore the factors that influence the survival of these patients.



## MATERIALS AND METHODS

### SEER database

From January 2004 to December 2016, demographic, clinicopathological, and follow-up data of patients who underwent surgery for the treatment of pNENs were extracted from the SEER database using SEER\*Stat software (version 8.3.5). The demographic data included age, race, and sex. The clinicopathological data included ICD-10 code, histology code, primary tumor location, tumor size, T, N, and M stages, pathologic grade, and surgery of the primary site. Survival data included survival months and vital status. Patients who underwent surgery other than pancreatectomy (local/partial resection, pancreaticoduodenectomy, or total pancreatectomy) were excluded.

### West China Hospital database

Patients who underwent surgery with curative intent in West China Hospital between January 2004 and December 2016 with pathologically confirmed pNEN were included. Demographic, clinicopathological, and follow-up data of patients were retrospectively retrieved from the West China Hospital database. Patients with mixed neuroendocrine-non neuroendocrine neoplasms were not included. Patients were excluded if there was not enough information to determine the functionality of the tumor ( $n = 16$ ). The follow-up deadline was August 2, 2019.

This study was approved by the West China Hospital Review Board under registration No. 2019 (124).

### Pathologic grade and stage

The pathologic grade was evaluated using mitotic count and Ki-67 index according to the World Health Organization (WHO) 2017 classification<sup>[12]</sup>. The TNM stage of tumor was assessed following the 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual<sup>[13]</sup>. Patients with pathologic grade unavailable and patients with G3 pancreatic neuroendocrine tumors (pNETs) or pancreatic neuroendocrine carcinomas (pNECs) (mitotic count > 20, Ki-67 index > 20%, and/or previously diagnosed G3 tumor) were excluded from further analysis.

### Functionality

Functionality was assessed according to whether hormone-related symptoms existed, regardless of the immunohistochemistry features. In addition to the nonfunctional pNEN group (N), functional pNENs were divided into two groups for further analysis: Insulinomas (I) and other functional pNENs (O).

### Statistical analysis

SPSS version 23.0 (IBM Corporation, Chicago, IL) was employed to perform statistical analyses, and  $P < 0.05$  was considered statistically significant. Continuous variables are reported in the form of the mean  $\pm$  SE and were compared using the Student's *t*-test. Nominal data (race, primary site of tumor, sex, *etc.*) are presented as frequencies and percentages and were compared using  $\chi^2$  tests or Fisher's exact tests. The primary end point of this study was overall survival, which was measured from the date of tumor diagnosis to the date of last follow-up or death. Patients with (1) primary tumor unevaluated (Tx), (2) grade unevaluated (Gx), and/or (3) mitotic count higher than 20 or Ki-67 index higher than 20% (NET G3 or NEC) were not involved in the subsequent statistical analysis. After verification of the proportional hazard assumption, Cox proportional hazard models were constructed to identify factors that predicted the prognosis. All variables with a  $P$  value < 0.1 in the univariate analysis were used as input variables for the multivariate analysis which was performed using a forward stepwise method.

## RESULTS

### Patient characteristics

From the SEER database, a total of 426 patients were enrolled in this study. The baseline data are shown in Table 1. The mean age was  $56.74 \pm 0.67$  years, and the male:female ratio was 221:205. There were 100 functional tumors (23.5%), including 52 insulinomas, 32 gastrinomas, 12 glucagonomas, 2 vipomas, and 2 somatostatinomas.

From the West China Hospital database, the mean age of the 205 patients was  $48.16 \pm 0.93$  years. There were 88 males (42.9%) and 117 females (57.1%). One hundred and

Table 1 Characteristics of patients in the two databases, *n* (%)

Database	SEER database ( <i>n</i> = 426)	West China Hospital database ( <i>n</i> = 205)	<i>P</i> value
Race			NC
White	357 (83.8)	0 (0.0)	
Asian <sup>1</sup>	25 (5.9)	205 (100)	
Others <sup>2</sup>	44 (10.3)	0 (0.0)	
Tumor site			< 0.001
Head	104 (24.4)	85 (41.5)	
Body	51 (12)	55 (26.8)	
Tail	168 (39.4)	44 (21.5)	
Unknown	103 (24.2)	21 (10.2)	
Age (yr)			< 0.001
0-55	193 (45.3)	138 (67.3)	
56-	233 (54.7)	67 (32.7)	
Sex			0.035
Male	221 (51.9)	88 (42.9)	
Female	205 (48.1)	117 (57.1)	
Primary tumor			0.030 <sup>3</sup>
T1	121 (28.4)	80 (39)	
T2	135 (31.7)	72 (35.1)	
T3	94 (22.1)	44 (21.5)	
T4	41 (9.6)	9 (4.4)	
Tx	35 (8.2)	0 (0)	
Regional lymph node metastasis			0.171 <sup>3</sup>
N0	188 (44.1)	41 (20)	
N1	149 (35)	22 (10.7)	
Nx	89 (20.9)	142 (69.3)	
Distant metastasis			0.044 <sup>3</sup>
M0	143 (33.6)	193 (94.1)	
M1	19 (4.5)	12 (5.9)	
Mx	264 (62)	0 (0)	
Grade			< 0.001 <sup>3</sup>
pNET G1	229 (53.8)	90 (43.9)	
pNET G2	45 (10.6)	96 (46.8)	
pNET G3 or pNEC	16 (3.8)	9 (4.4)	
Gx	136 (31.9)	10 (4.9)	
Functionality			< 0.001
N	326 (76.5)	101 (49.3)	
I	52 (12.2)	85 (41.5)	
O	48 (11.3)	19 (9.3)	
Surgery			< 0.001 <sup>3</sup>
Pancreaticoduodenectomy	143 (33.6)	39 (19)	



Total pancreatectomy	39 (9.2)	6 (2.9)
Partial pancreatectomy	203 (47.7)	88 (42.9)
Local excision	38 (8.9)	72 (35.1)
Other surgeries	3 (0.7)	0 (0)

<sup>1</sup>Consisting of Asian and Pacific Islander patients.

<sup>2</sup>Consisting of Black and American Indian patients and patients whose races were unknown.

<sup>3</sup>Rows with the title Tx, Nx, Mx, Gx, and other surgeries were not involved in the  $\chi^2$  test. SEER: Surveillance, epidemiology, and end results; NC: Not comparable; pNET: Pancreatic neuroendocrine tumor; pNEC: Pancreatic neuroendocrine carcinoma; I: Insulinoma; N: Nonfunctional pNEN; O: Other functional pNEN.

four (50.7%) patients had functional tumors including 85 insulinomas, 9 gastrinomas, 7 glucagonomas, 1 vipoma, 1 somatostatinoma, and 1 rare pNEN secreting adrenocorticotrophic hormone (ACTH)<sup>[14]</sup>. Compared with the SEER database, patients in the West China Hospital database had fewer tumors of the pancreatic tail, were younger, had a lower T stage, fewer G2 tumors, and fewer distant metastases, and had more female patients ( $P < 0.05$ ). Although the N stage was comparable in the two databases, the West China Hospital database had more patients with unevaluated N stage (Nx).

When we compared the characteristics of patients of different races (Table 2), the difference between the White and Asian populations was similar to the difference between the two datasets. In the other races, the ratio of male patients was higher, and the proportion of G3 pNETs or pNECs was higher than the respective values in the White and Asian populations. Survival curves of patients of different races from the two databases are shown in Figure 1.

### Prognostic factors

Contemporaneous data from the two databases were analyzed separately as two cohorts and then merged as the third cohort to create a larger sample that was suitable for the univariate and multivariate analyses. Patients of races other than White or Asian and Pacific Islander, patients with primary tumor not assessed (Tx) or pathologic grade unevaluated (Gx), and patients who had G3 pNETs or pNECs were not enrolled in the subsequent analysis due to the limitations of the Cox regression model.

The univariate and multivariate analyses of the SEER cohort and the West China Hospital cohort are shown in Table 3. The two cohorts displayed similarities in the hazard ratios (HRs) of age, sex, T stage, regional lymph node metastasis, and distant metastasis, but showed differences in the HRs of primary site, grade, and functionality. In the multivariate analysis, the results of the SEER cohort showed that age (HR = 2.203, 95%CI: 1.249-3.884,  $P = 0.006$ ) and T stage (HR = 2.589, 95%CI: 1.533-4.371,  $P < 0.001$ ) were independent risk factors for predicting prognosis. The results of the West China Hospital cohort showed that age (HR = 4.558, 95%CI: 1.122-18.521,  $P = 0.034$ ), sex (HR = 5.707, 95%CI: 1.161-28.057,  $P = 0.032$ ), and grade (HR = 9.039, 95%CI: 1.118-73.051,  $P = 0.039$ ) were independent prognostic factors.

In the cohort consisting of the combined populations from the two databases, factors that affected prognosis in the univariate analysis included country ( $P = 0.002$ ), race ( $P = 0.001$ ), age ( $P < 0.001$ ), sex ( $P = 0.005$ ), T stage ( $P < 0.001$ ), regional lymph node metastasis (N1,  $P = 0.036$ ), distant metastasis ( $P < 0.001$ ), and functionality (nonfunctional pNETs,  $P = 0.031$ ; other functional pNETs,  $P = 0.012$ ). The multivariate proportional hazard model contained only race (HR = 0.438, 95%CI: 0.225-0.851,  $P = 0.015$ ), age (HR = 2.315, 95%CI: 1.362-3.935,  $P = 0.002$ ), sex (HR = 1.744, 95%CI: 1.049-2.899,  $P = 0.032$ ), and T stage (HR = 2.612, 95%CI: 1.603-4.254,  $P < 0.001$ ).

### Effect of functionality on survival

In the West China Hospital database and in the total population, nonfunctional pNETs (West China Hospital database: HR = 1.473, 95%CI: 0.268-8.092,  $P = 0.656$ ; total population: HR = 2.544, 95%CI: 1.090-5.938,  $P = 0.031$ ) and other functional pNETs (West China Hospital database: HR = 7.913, 95%CI: 1.314-47.670,  $P = 0.024$ ; total population: HR = 3.925, 95%CI: 1.359-11.337,  $P = 0.012$ ) tended to have poorer prognoses than insulinoma. However, as shown in the multivariate analysis, functionality was not associated with the survival time of patients with pNETs since it was not selected into the model.

Table 2 Characteristics of patients of different races, *n* (%)

Race	White ( <i>n</i> = 357)	Asian <sup>1</sup> ( <i>n</i> = 230)	Others <sup>2</sup> ( <i>n</i> = 44)	<i>P</i> value
Tumor site				< 0.001
Head	80 (22.4)	94 (40.9)	15 (34.1)	
Body	40 (11.2)	59 (25.7)	7 (15.9)	
Tail	153 (42.9)	48 (20.9)	11 (25)	
Unknown	84 (23.5)	29 (12.6)	11 (25)	
Age (yr)				< 0.001
0-55	156 (43.7)	150 (65.2)	25 (56.8)	
56-	201 (56.3)	80 (34.8)	19 (43.2)	
Sex				0.002
Male	162 (45.4)	130 (56.5)	30 (68.2)	
Female	195 (54.6)	100 (43.5)	14 (31.8)	
Primary tumor				0.073 <sup>3</sup>
T1	98 (27.5)	89 (38.7)	14 (31.8)	
T2	117 (32.8)	79 (34.3)	11 (25)	
T3	79 (22.1)	51 (22.2)	8 (18.2)	
T4	35 (9.8)	10 (4.3)	5 (11.4)	
Tx	28 (7.8)	1 (0.4)	6 (13.6)	
Regional lymph node metastasis				0.094 <sup>3</sup>
N0	157 (44)	53 (23)	19 (43.2)	
N1	128 (35.9)	25 (10.9)	18 (40.9)	
Nx	72 (20.2)	152 (66.1)	7 (15.9)	
Distant metastasis				0.054 <sup>3</sup>
M0	119 (33.3)	202 (87.8)	15 (34.1)	
M1	16 (4.5)	12 (5.2)	3 (6.8)	
Mx	222 (62.2)	16 (7)	26 (59.1)	
Grade				< 0.001 <sup>3</sup>
pNET G1	192 (53.8)	105 (45.7)	22 (50)	
pNET G2	42 (11.8)	98 (42.6)	1 (2.3)	
pNET G3 or pNEC	13 (3.6)	9 (3.9)	3 (6.8)	
Gx	110 (30.8)	18 (7.8)	18 (40.9)	
Functionality				< 0.001
N	277 (77.6)	117 (50.9)	33 (75)	
I	40 (11.2)	93 (40.4)	4 (9.1)	
O	40 (11.2)	20 (8.7)	7 (15.9)	
Surgery				< 0.001 <sup>3</sup>
Pancreaticoduodenectomy	111 (31.1)	51 (22.2)	20 (45.5)	
Total pancreatectomy	33 (9.2)	7 (3)	5 (11.4)	
Partial pancreatectomy	179 (50.1)	96 (41.7)	16 (36.4)	
Local excision	31 (8.7)	76 (33)	3 (6.8)	
Other surgeries	3 (0.8)	0 (0)	0 (0)	

<sup>1</sup>Consisting of Asian and Pacific Islander patients.

<sup>2</sup>Consisting of Black and American Indian patients and patients whose races were unknown.

<sup>3</sup>Rows with the title Tx, Nx, Mx, Gx and other surgeries were not involved in the chi-square test. pNET: Pancreatic neuroendocrine tumor; pNEC: Pancreatic neuroendocrine carcinoma; I: Insulinoma; N: Nonfunctional pNEN; O: Other functional pNEN.

## DISCUSSION

Compared with pancreatic ductal adenocarcinoma, pNETs are characterized by a lower incidence, younger age, and better prognosis<sup>[1]</sup>. According to morphological features, the WHO 2017 guidelines divide pNENs into biologically different groups, pNETs and pNECs. pNET cells have a fairly uniform, solid, trabecular, spiral or glandular patterned nucleus with pepper-salt chromatin and granular cytoplasm, while pNECs are similar to small or large cell neuroendocrine carcinomas of the lung<sup>[15]</sup>. Only pNETs can be divided into three different prognostic groups (G1, G2, and G3) according to mitotic count and Ki-67 index. Subsequently, the AJCC updated the staging system of pancreatic tumors<sup>[13]</sup>. PNET G1 and G2 are staged in a scheme that is similar to the European Neuroendocrine Tumor Society Consensus Guidelines staging system<sup>[16,17]</sup>, while G3 pNETs and pNECs share the same staging system as pancreatic exocrine tumors.

pNENs were previously classified into several groups according to the existence and type of hormone related symptoms. The group, or rather, functionality was believed to be associated with the survival of patients with pNEN. Cienfuegos *et al*<sup>[4]</sup> performed a log-rank survival analysis on pNEN patients, and the results showed that the nonfunctioning tumor group had a relatively poor prognosis compared with the functioning tumor group ( $P = 0.052$ ). Studies have indicated that functionality is positively related to the expression of somatostatin receptor 2<sup>[18]</sup> and negatively related to aurora kinase B<sup>[19]</sup>, which may contribute to the improvement in survival. Wang *et al*<sup>[5]</sup> and Nanno *et al*<sup>[6]</sup> found that functionality is a prognostic factor affecting overall survival and disease-free survival in the results of univariate Cox regression analysis. However, the multivariate analysis was not carried out in the study by Wang *et al*<sup>[5]</sup> (due to the small sample size) and did not include functionality as a factor in the model in the study by Nanno *et al*<sup>[6]</sup> (only venous invasion and grade were used as input variables).

In recent years, studies have proposed new viewpoints. Studies<sup>[20,21]</sup> that included patients with NENs in almost all the locations suggested that functionality is not associated with progression-free survival<sup>13</sup> or disease-free survival<sup>[14]</sup>. However, there are differences in biological characteristics between NENs of lung origin and gastroenteropancreatic NENs: The majority of the functional NENs are carcinoid syndrome<sup>[20]</sup>, while the functional tumors of gastroenteropancreatic NENs, especially pNENs, are mainly insulinomas<sup>[10]</sup>.

Our results indicated that race, age, sex, and T stage were independent factors for predicting the survival of patients with pNETs. Although no significant differences were found in the effects of some factors on survival in the small sample cohorts, it does not mean that there is no relationship between these factors and survival. Only a sample that is large enough can reveal the real prognostic factor.

Functionality was correlated with survival in the univariate analysis, but was not associated with prognosis in the multivariate analysis. The prognosis of patients with nonfunctional tumors is generally considered to be poorer than that of patients with insulinoma. However, this is more likely related to the late diagnosis of patients with nonfunctional tumors, rather than the difference in biological properties between functional and nonfunctional tumors or the effect of hormones secreted by functional tumors. Hormone related syndrome is the only basis to distinguish between the nonfunctional neuroendocrine neoplasm and several types of functional neuroendocrine neoplasm. However, immunohistochemical staining also shows the expression of insulin/glucagon/gastrin/somatostatin in non-functional tumors. The reasonability of classification based on symptoms rather than gene expression needs to be further explored.

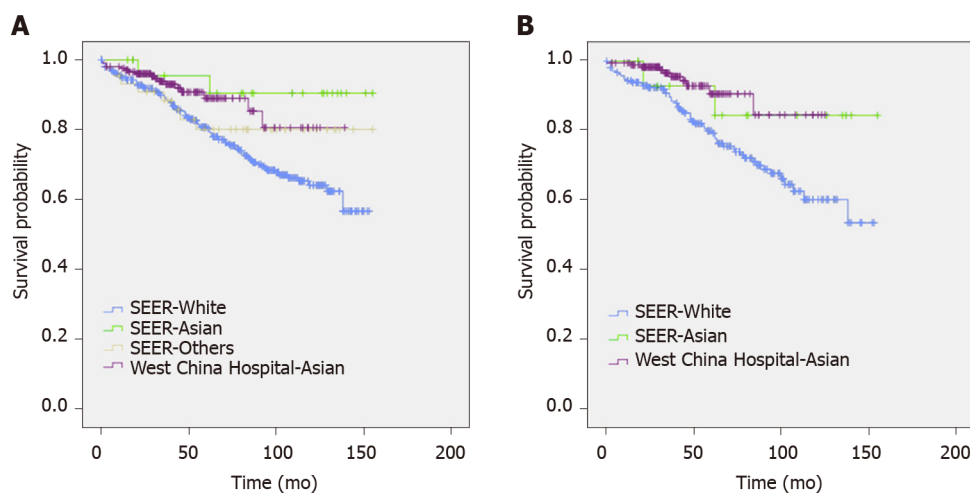
According to WHO guidelines, the assessment of grade depends on mitotic count and Ki-67 index, with a cutoff value of 2/10 high power fields and 3%, respectively. However, the cutoff values that make the most sense are still debatable. Some studies support that Ki-67 and mitotic count is correlated with prognosis<sup>[6,11]</sup>, while there are also some studies that do not support this viewpoint<sup>[18]</sup>. In the Western China Hospital database, grade is an independent risk factor for prognosis. But in the SEER database, grade is not related to prognosis.

**Table 3 Univariate and multivariate Cox proportional hazard regression analyses of predictors of survival in patients**

Study population		SEER database		West China Hospital database		All population	
Variables		HR (95CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
<b>Univariate analysis</b>							
Country							
United States						1.000	
China						0.326 (0.159, 0.665)	0.002
Race							
White	1.000					1.000	
Asian	0.402 (0.098, 1.652)	0.206				0.326 (0.169, 0.626)	0.001
Age (yr)							
Below 55	1.000			1.000		1.000	
Over 56	2.121 (1.204, 3.738)	0.009		4.224 (1.055, 16.919)	0.042	2.710 (1.606, 4.574)	< 0.001
Sex							
Female	1.000			1.000		1.000	
Male	1.822 (1.065, 3.119)	0.029		4.262 (0.878, 20.686)	0.072	2.067 (1.251, 3.415)	0.005
Primary site							
Head	1.000			1.000		1.000	
Body	2.077 (0.899, 4.800)	0.087		0.801 (0.146, 4.398)	0.799	1.651 (0.784, 3.479)	0.187
Tail	1.259 (0.616, 2.573)	0.527		1.193 (0.266, 5.349)	0.817	1.445 (0.769, 2.718)	0.253
Unknown	1.359 (0.598, 3.085)	0.464		0.000	0.987	1.491 (0.698, 3.187)	0.303
Primary tumor							
T1-2	1.000			1.000		1.000	
T3-4	2.515 (1.490, 4.246)	0.001		3.663 (0.980, 13.688)	0.054	2.858 (1.756, 4.651)	< 0.001
Regional lymph node metastasis							
N0	1.000			1.000		1.000	
N1	1.602 (0.918, 2.795)	0.097		2.757 (0.387, 19.630)	0.311	1.775 (1.040, 3.032)	0.036
Nx	0.911 (0.407, 2.038)	0.820		0.981 (0.186, 5.170)	0.982	0.585 (0.293, 1.167)	0.128
Distant metastasis							
M0	1.000			1.000		1.000	
M1	5.295 (1.804, 15.543)	0.002		3.423 (0.423, 27.705)	0.249	5.726 (2.269, 14.450)	< 0.001
Mx	1.993 (0.973, 4.079)	0.059				2.773 (1.551, 4.960)	0.001
Grade							
G1	1.000			1.000		1.000	
G2	1.418 (0.734, 2.739)	0.298		9.823 (1.224, 78.806)	0.032	1.266 (0.740, 2.166)	0.388
Functionality							
I	1.000			1.000		1.000	
N	1.924 (0.691, 5.353)	0.210		1.473 (0.268, 8.092)	0.656	2.544 (1.090, 5.938)	0.031
O	2.247 (0.600, 8.423)	0.230		7.913 (1.314, 47.670)	0.024	3.925 (1.359, 11.337)	0.012
<b>Multivariate analysis</b>							
Race							
White						1.000	
Asian						0.438 (0.225, 0.851)	0.015

Age									
Below 55	1.000			1.000			1.000		
Over 56	2.203	(1.249, 3.884)	0.006	4.558	(1.122, 18.521)	0.034	2.315	(1.362, 3.935)	0.002
Sex									
Female				1.000			1.000		
Male				5.707	(1.161, 28.057)	0.032	1.744	(1.049, 2.899)	0.032
Primary tumor									
T1-2	1.000						1.000		
T3-4	2.589	(1.533, 4.371)	< 0.001				2.612	(1.603, 4.254)	< 0.001
Grade									
G1				1.000					
G2				9.039	(1.118, 73.051)	0.039			

SEER: Surveillance, epidemiology, and end results; I: Insulinoma; N: Nonfunctional pNEN; O: Other functional pNEN.



**Figure 1** Survival functions of patients by database and race. A: Survival of patients enrolled; B: Survival of patients analyzed. SEER: Surveillance, epidemiology, and end results.

There was a trend of shorter survival time for patients with higher T stage in our small-sample cohort ( $n = 205$ ), and T stage turned out to be an independent prognostic factor in large-sample cohorts (SEER,  $n = 426$ ; total,  $n = 631$ ), which is similar to the results of other studies<sup>[6,21]</sup>. On one hand, it indicated that T stage is indeed a factor that affects the prognoses of patients with pNETs; on the other hand, the results showed the importance of sample size in cohort study.

Data of the same period from the two databases were included in the analyses above. The distributions of N stage were comparable between the two datasets, but the populations from the two databases had differences in the distributions of primary tumor location, age, sex, T stage, M stage, grade, functionality, and surgery. Compared with the data in the SEER database (Table 1) and the results from other studies<sup>[4,5]</sup>, the proportion of nonfunctional tumors was only approximately 50% in the West China Hospital database, indicating that some patients were not diagnosed and treated and that there is a need to advance the screening and early diagnosis of nonfunctional pNENs. Insulinomas accounted for only half of the functional tumors in the SEER database, while insulinomas accounted for the vast majority of functional pNENs in the West China Hospital database, which is similar to the results of Wang *et al.*<sup>[9]</sup>. Local excision was performed more commonly in the West China Hospital database, especially before 2010, which led to a higher proportion of patients with no lymph nodes examined (Nx).

There were some limitations to this study: (1) Patients of the same time period were

enrolled from the two databases, and the inclusion/exclusion criteria were the same. However, SEER is a multicenter database, while the West China Hospital database is a single center database. The baseline data of the two datasets had differences in the distributions of some variables. Most of the data were demographic data or objective clinical data (such as tumor size and lymph node metastasis). The tumor grade depends on the mitotic count and Ki-67 index whose implementation may vary in different centers. Cox regression of the combined dataset may not represent the relationship between grade and prognosis; and (2) This study collected data from 2004 to 2016 retrospectively, and there is not sufficient information to separate poorly-differentiated pNECs from well-differentiated G3 pNETs in the SEER database. The TNM stages of G3 pNETs and pNECs may not have the same effect on survival as those of G1 and G2 tumors since they are completely different stage systems. Therefore, we excluded all tumors with mitotic counts higher than 20 or Ki-67 indexes higher than 20% (G3 pNETs and pNECs).

## ARTICLE HIGHLIGHTS

### **Research background**

Pancreatic neuroendocrine neoplasms (pNENs) that produce hormones leading to symptoms are classified as functional tumors, while others are classified as nonfunctional tumors.

### **Research motivation**

The traditional view is that functionality affects the prognosis of pNEN patients. However, recent studies have proposed new viewpoints. Because of the rarity of pNENs and the low proportion of functional tumors, few studies have performed multivariate Cox regression to show the effect of functionality on survival.

### **Research objectives**

To assess whether functionality is an independent factor for predicting the prognosis of pNEN patients.

### **Research methods**

From January 2004 to December 2016, data of patients who underwent surgery at the primary site for the treatment of pNENs from the Surveillance, Epidemiology, and End Results (SEER) database and West China Hospital database were retrospectively analyzed.

### **Research results**

From the SEER database, age and T stage were independent risk factors affecting the survival. From the West China Hospital database, independent prognostic factors were age, sex, and grade. The result of the cohort consisting of the combined populations from the two databases showed that race, age, sex, and T stage were independent prognostic factors. In the West China Hospital database and in the total population, nonfunctional pNETs and other functional pNETs tended to have poorer prognoses than insulinomas. However, functionality was not associated with the survival time of patients with pNETs in the multivariate analysis.

### **Research conclusions**

Race, age, sex, and T stage are independent factors for predicting the survival of patients with pNETs. The results of this study do not support the opinion that hormone related syndrome is an efficacious tool to classify tumors into groups with different prognoses.

### **Research perspectives**

Hormone related syndrome is the only basis to assess the functionality of neuroendocrine neoplasms. Nonfunctional tumors and functional tumors were reported to have different prognoses. However, they do not have much difference in pathologic feature or gene expression. Immunohistochemical staining also displays the expression of insulin/glucagon/gastrin/somatostatin in non-functional tumors. The reasonability of classification based on symptoms rather than gene expression needs to be further explored.



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