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Original Research

Pancreatic neuroendocrine tumours: Grade is superior to T, N, or M status in predicting outcome and selecting patients for chemotherapy:A retrospective cohort study in the SEER database

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ABSTRACT

Background: Pancreatic neuroendocrine tumours (pNETs) are a rare and heterogeneous group of tumours with an increasing incidence. Current staging criteria for pNETs remain limited and controversial. Meanwhile, the impact of chemotherapy on overall survival has not been fully defined.
Objectives: The current study aimed to explore epidemiologic trends of pancreatic neuroendocrine tumours (pNETs). To determine feasible improvements to staging criteria and investigate the relationship between chemotherapy and survival.
Methods: A retrospective cohort study design was used to analyse annual cancer incidence rates, patient demographics, tumour site and stage, and treatment of pNETs. Data were obtained from the National Cancer Institute's SEER registry for all patients diagnosed with pNETs between January 1973 and December 2015.
Results: Patients diagnosed after 2010 were more likely to present with age greater than 45 years, T0, T1 status, N0 status, M0 status, and well differentiation. Current AJCC staging criteria was applicable to patients with well differentiation, but not other differentiation. The revised system, defined by Grade, T, N, and M status, could robustly discriminate between survival curves. Chemotherapy was associated with significantly improved survival for patients with poorly differentiated and undifferentiated tumour grading.
Conclusions: Grade is superior to 'T', 'N', or 'M' status in predicting outcomes and selecting patients for chemotherapy. It is necessary and feasible to combine grade into current staging criteria.

1. Introduction

Pancreatic neuroendocrine tumours (pNETs) are a rare and heterogeneous group of tumours with an increasing incidence [1,2]. The increase in pNET incidence could be related to a higher number of diagnoses made through imaging studies, which can have a greater sensitivity to detecting this disease [3,4]. However, current staging criteria (both the European Neuroendocrine Tumour Society (ENETS) and the American Joint Committee on Cancer (AJCC) staging criteria) for pNETs remain limited and controversial; thus different recommendations for staging modifications or nomograms have been proposed [5–9].

It also was revealed that the classic 'T' and 'N' stage failed to show independent prognostic significance in gastroenteropancreatic neuroendocrine neoplasms, whereas tumour differentiation is the most significant prognostic metric for disease course and progression [7,10]. Moreover, it has been recommended that the study of how the combination of tumour stage and grade aid in predict outcomes in patients is needed [5]. Tumour resection is associated with improved long-term survival for all stages [11]. In the ENETS consensus guidelines, chemotherapy is recommended for pNETs with distant metastases of any grade [12]; however, strong evidence for treatment efficacy of chemotherapy, did not exist. Even though the treatment for neuroendocrine tumours (NETs) has entered the era of 'targeted therapy', the role of chemotherapy continues to be debated.

Considering these controversies regarding staging criteria and the therapeutic management of pNETs, we aimed to investigate the following: (1) perform a population-based evaluation of secular trends in

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pNET incidence and identify associative factors; (2) examine the impact of classic 'T', 'N', 'M' staging and grading on overall survival (OS); and (3) determine whether chemotherapy has a survival benefit for this patient population.

2. Materials and methods

2.1. Data source

We performed a retrospective cohort study of patients with pNETs using the Surveillance, Epidemiology, and End Results (SEER) database based on the November 2015 submissions. The National Cancer Institute's SEER program collects data on patient demographics, morphology, stage, and treatment. This registry also provides information on cancer incidence and survival for approximately 28% of the US population. Patients were retrieved based on the International Classification of Diseases for Oncology (2nd and 3rd editions) codes for tumours of the pancreas: C25.0 to C25.9. This study has been reported in line with the STROCSS criteria.[13] The following International Classification of Diseases for Oncology (3rd edition) diagnosis codes were included: islet-cell adenocarcinoma (8150), malignant beta-cell tumour (8151), malignant alpha-cell tumour (8152), G-cell tumour (8153), Mixed islet cell and exocrine tumour (8154), VIPoma (8155), malignant somatostatinoma (8156), malignant enteroglucagonoma (8157), carcinoid tumour (8240), argentaffin carcinoid tumour (8241), enterochromaffin cell tumour (8242), mucocarcinoid tumour (8243), Goblet carcinoid tumour (8244), neuroendocrine carcinoid (8246), and atypical carcinoid tumour (8249). Patients identified through autopsy and death certificates were excluded. The demographics and patient characteristics included the extent of disease (local, regional, or distant), size of the primary tumour, nodal status, age, race, sex, survival time in months, and vital status. We coded T, N, and M status according to a combination of clinical, surgical, and pathological assessment.

2.2. Statistical analysis

To evaluate factors associated with incidence, we calculated the 1973–2015 incidences using SEER18. A univariate statistical analysis was performed using the Chi-square test as indicated.

To compute age-standardized incidence rates per 100,000 person-years, we calculated the 1973–2015 incidences using the older SEER9 data for a better understanding of longitudinal changes in incidence over time. To determine the time point at which the incidence trends changed, joinpoint regression models were used via JoinPoint regression analysis Software (JoinPoint Trend Analysis Software, version 4.6.0.0, April 2018; US National Cancer Institute, Bethesda, MD, USA) [10]. Data were modelled using an algorithm to select the optimal number of inflection points where incidence rates changed in either direction or magnitude, which limited the maximum number of joinpoints to 5 [14]. The log-transformed slopes are expressed as annual percentage change (APC), which represents trends in cancer rates across time. The predicted annual incidence rates were calculated based on the estimated APC by sex and cancer site, and were assumed to change at a constant percentage of the rate from the previous year.

To investigate independent prognostic factors and the relationship between chemotherapy and survival, we recalculated the 1973–2013 incidences using SEER18. The following variables were exported from SEER*Stat 8.3.5 software to Excel (Microsoft Corp., Redmond, WA, USA) for further analysis: sex, age at diagnosis, race, tumour size, extension (extension to peripancreatic tissue or adjacent structures), tumour grade, year of diagnosis, N and M status, surgery at the primary site, and whether chemotherapy was administered. Data with missing values were excluded from the statistical analysis. A total of 1847 patients with pNETs were selected for further analysis. The Kaplan-Meier method and the log-rank test were used for the univariate survival analysis, and Cox hazard regression modelling was used for the multivariate survival analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Propensity score-matching analysis was performed to consider the high hazard ratio characteristics of the Cox analysis. Patients who received chemotherapy were matched to patients who did not with an algorithm of the nearest neighbor 1:1 matching [15]. Discrimination was evaluated using a concordance index (C-index), which quantifies the probability that of two random patients, the patient who relapses first had a higher probability of the event of interest. All statistical analyses were performed with SPSS statistics software (version 25.0.0, IBM Corp, Armonk, NY, USA) and R version 2.13.2 (http://www.r-project.org). $P < 0.05$ was considered statistically significant for all analyses.

3. Results

3.1. Annual incidence

From 1973 to 2009, a total of 4208 patients were diagnosed with pNET in the SEER9 registry. The incidence rate increased 6.1-fold from 1973 (0.17 per 100,000) to 2015 (1.03 per 100,000). In 2015, the pNET incidence was 0.9 per 100,000 in females, and 1.2 per 100,000 in males. The pNET incidence rate increased by 8.20% (95% CI: 7.6–8.8) between 1996 and 2015. Moreover, the pNET incidence rate increased by 9.94% (95% CI: 8.6–11.3) after 2000 for females and 7.55% (95% CI: 7.0–8.1) after 1993 in males (Supplementary Fig. S1). The APC-based predicted incidence rate of pNET between 2016 and 2025 are shown in Supplementary Fig. S1B. Based on the predictive model, the incidence rate of pNET will continue to increase. By 2025, the incidence rate is projected to increase to 2.23 per 100,000 in females and 2.48 per 100,000 in males.

3.2. Demographics by era

A total of 7384 patients with pNETs were identified (Table 1). A majority of the patients were Caucasian (79.23%), male (54.48%), aged older than 45 years (83.92%), and had N0 disease status (67.73%). For comparison purposes, 3 time-based groups were created: 2010–2015 (era 1), 2004–2009 (era 2), and 1973–2003 (era 3). Partial data for patients diagnosed in era 3 are unrecorded. According to the univariate analysis (Table 1), patients in era 1 were more likely to present with an age older than 45 years (86.09% *vs.* 84.21% *vs.* 79.60%; $P < 0.001$), T0 or T1 status (28.84% *vs.* 10.87%; $P < 0.001$), N0 status (70.44% *vs.* 58.63%; $P < 0.001$), M0 status (62.13% *vs.* 39.31%; $P < 0.001$), well differentiation (68.98% *vs.* 57.72% *vs.* 32.09%; $P < 0.001$). In addition, patients in era 1 were less likely to present with poor and undifferentiated tumour grade (11.35% *vs.* 21.07% *vs.* 41.82%; $P < 0.001$).

When comparing era 1 and era 3, there was a 370% increase in patients presenting with well differentiation (odds ratio, 4.706; $P < 0.001$), and an 80% decrease in patients presenting with poor and undifferentiated tumour grade (odds ratio, 0.178; $P < 0.001$). A similar pattern was found for M status. A male preponderance (54.48%) was observed in all eras, but this gap was predicted to gradually decrease over time (Table 1, Supplemrntary Fig. S1B). Interestingly, the quantity of patients with functioning pNETs (120 *vs.* 107) essentially remained stable and was small between era 1 and era 2.

3.3. Independent prognostic factors

To investigate independent prognostic factors, we recalculated the 1973–2013 incidences using SEER18 and excluded patients with missing information on stage, race/ethnicity, age, histology, and treatment.

We identified 1846 patients with pNETs and complete data. Multivariate analysis with Cox regression of the pNETs was performed and the following factors were found to have a negative influence on

Table 1
Pancreatic neuroendocrine tumours patient demographics by era, SEER18 registry, 1973–2015.

Factor	2010–2015 (n = 3658)	2004–2009 (n = 1780)	1973–2003 (n = 1946)	P value	Overall population
Age				< 0.001	
≥45	86.09% (3149)	84.21% (1499)	79.60% (1549)		83.92%
≤44	13.91% (509)	15.79% (281)	20.40% (397)		16.08%
Sex				.3038	
Male	55.44% (2028)	53.37% (950)	53.70% (1045)		54.48%
Female	44.56% (1630)	46.63% (830)	46.30% (901)		45.52%
T status				< .001	
T0,T1	28.84% (906)	10.87% (104)	–		24.64%
T2	35.49% (1115)	34.80% (333)	–		35.33%
T3	27.88% (876)	37.20% (356)	–		30.06%
T4	7.80% (245)	17.14% (164)	–		9.98%
unknow	(516)	(823)	(1946)		
N status				< .001	
N0	70.44% (2350)	58.63% (584)	–		67.73%
N1	29.56% (986)	41.37% (412)	–		32.27%
unknow	(322)	(784)	(1946)		
M status				< .001	
M0	62.13% (2272)	39.31% (476)	–		56.45%
M1	37.87% (1385)	60.69% (735)	–		43.55%
unknow	(1)	(569)	(1946)		
Grade				< .001	
G1	68.98% (1690)	57.72% (441)	32.09% (155)		61.83%
G2	19.67% (482)	21.20% (162)	26.09% (126)		20.83%
G3 + G4	11.35% (278)	21.07% (161)	41.82% (202)		17.34%
unknow	(1208)	(1016)	(1463)		
Extension				< .001	
Exten	43.06% (1575)	59.33% (1056)	–		48.38%
Unexten	56.94% (2083)	40.67% (724)	–		51.61%
unknow	–	–	(1946)		
Function				< .001	
functional	3.28% (120)	6.01% (107)	8.94% (174)		5.43%
Non	96.72% (3538)	93.99% (1673)	91.06% (1772)		94.57%
Race				< .001	
White	76.82% (2810)	79.49% (1415)	83.50% (1625)		79.23%
Other	23.18% (848)	20.51% (365)	16.50% (321)		20.77%

survival: early year of diagnosis, male, age ≥45 years, non-functional histologic type, poor and undifferentiated tumour grade, tumour size > 2 cm, as well as N1, M1, and extensional disease (Table 2). Tumour size of 2–4 cm and > 4 cm had similar HRs (1.624 *vs.* 1.598). Marital status, chemotherapy treatment, and insurance status were not found to be independently predictive of survival (P = 0.059, P = 0.654, and P = 0.211, respectively). Of all the independent prognostic factors, tumour grade (HR, 4.430; 95% CI: 3.565–5.504; P < 0.001) and surgery (HR, 3.730; 95% CI: 2.988–4.657; P < 0.001) were found to be the most significant prognostic metrics.

Given the significance of tumour grade/differentiation, we calculated the independent prognostic factors for each grade. Sex, extensional status, and histologic type were not prognostic in patients with G1 status. M status and surgery were the only 2 significant risk factors of survival in patients with G2 status. Year of diagnosis, sex, age, race, and tumour size failed to show independent prognostic significance in patients with G3/G4 status. In general, M status and surgery were the only 2 independent prognostic factors of each subcategory for tumour grade.

3.4. Modified staging classification for pNETs

Supplemrntary Fig. S3 shows survival estimates by AJCC TNM classification for patients with different grade. In patients with G1 status, survival curves of adjacent stages were well-separated except for stage III. Whereas, in patients with G2 and G3/G4 status, It is notable that overlap existed among the AJCC classification of each stage. This phenomenon can be explained by the above Cox analysis that tumour size and N status were significant prognostic metrics and had a relatively high risk ratio in patients with G1 status but not G2 or G3/G4 status. Therefore, the shortcoming of the previous staging is that the Grade classification is not considered.

A modified staging classification defined by Grade, as well as T, N, and M status was proposed (Fig. 1). Survival curves were well-separated between disease stage for the new classification. Given surgery is an important confounding factor and the fact that we had a small sample size of patients not receiving surgery, non-surgical patients were excluded. The modified staging classification had a higher predictive ability with a C-index of 0.77, whereas the C-index of AJCC TNM classification was 0.73. Furthermore, the proportion of patients with stage III disease using the modified system was higher than that of the AJCC system (20.6% v 2.2%).

3.5. Patients demographics according to chemotherapy

Of all the 1847 patients with pNETs, 336 patients (18.19%) were treated with adjuvant chemotherapy (Supplementary Table S1). Patients who underwent chemotherapy were diagnosed at an early disease stage (P = 0.004), and had tumours of lower grade (P < 0.001) and larger size (P < 0.001). Patients who have lymphatic metastasis, extension, distant metastases, and medical insurance were more likely to be treated with chemotherapy (all P values < 0.001). Patients who received surgery were less likely to accept chemotherapy (86% *vs.* 44%, P < 0.001).

3.6. Effect of chemotherapy

Interestingly, although chemotherapy does not show prognostic effect in pNETs as a whole, it does offer a better prognosis to patients with poor and undifferentiated tumour grade (HR, 0.598; 95% CI: 0.429–0.834; P = 0.002), but a worse prognosis for patients with high differentiation (HR, 1.436; 95% CI: 1.016–2.031; P = 0.041) (Table 2).

Table 2
Multivariable Survival Analysis of Patients With pNETs Diagnosed From 1973 to 2013, SEER18 registry.

Covariate	Total pNETs (n = 1846)		G1 (n = 1243)		G2 (n = 346)		G3 + G4 (n = 257)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Year								
2010–2013	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
1973–2009	1.339 (1.082–1.657)	0.008	1.368 (1.001–1.869)	0.049	1.208 (0.681–2.142)	0.471	1.281 (0.864–1.900)	0.218
Sex								
Female	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Male	1.269 (1.060–1.519)	0.009	1.305 (0.992–1.717)	0.057	1.274 (0.843–1.927)	0.251	1.151 (8.843–1.570)	0.376
Age								
≤44	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
≥45	1.627 (1.230–2.152)	< .001	2.202 (1.341–3.045)	0.001	1.796 (0.966–3.338)	0.064	1.057 (0.568–1.966)	0.218
Marital status								
Married	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Other	1.193 (0.903–1.434)	0.059	1.287 (0.977–1.697)	0.073	1.164 (0.747–1.815)	0.502	1.092 (0.797–1.495)	0.584
Race								
White	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Other	0.922 (0.745–1.141)	0.456	0.639 (0.453–0.900)	0.011	1.011 (0.598–1.710)	0.967	1.298 (0.922–1.827)	0.135
Histologic type								
functional	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
nonfunctional	2.054 (1.381–3.056)	< .001	1.316 (0.576–3.005)	0.515	1.696 (0.783–3.670)	0.18	3.381 (1.742–6.321)	< 0.001
Grade		< .001	NA		NA		NA	
G1	1 [Reference]							
G2	1.298 (1.027–1.641)	0.029						
G3/G4	4.430 (3.565–5.504)	< .001						
Size		0.012		0.019		0.577		0.351
< 2 cm	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
2–4 cm	1.624 (1.166–2.262)	0.004	1.833 (1.144–2.937)	0.012	0.785 (0.369–1.672)	0.531	1.309 (0.697–2.458)	0.402
> 4 cm	1.589 (1.143–2.208)	0.006	1.960 (1.216–1.216)	0.006	0.990 (0.479–2.050)	0.979	1.057 (0.568–1.966)	0.862
Node status								
N0	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
N1	1.373 (1.146–1.644)	< .001	1.600 (1.196–2.140)	0.002	1.099 (0.728–1.659)	0.654	1.394 (1.025–1.896)	0.034
Extension								
Unextensional	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Extensional	1.302 (1.007–1.681)	0.044	1.174 (0.739–1.866)	0.497	1.454 (0.764–2.767)	0.255	1.453 (1.005–2.101)	0.047
Metastasis								
Non-metas	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Metastatic	2.141 (1.744–2.628)	< .001	2.265 (1.626–3.156)	< .001	1.711 (1.099–2.662)	0.017	1.839 (1.299–2.605)	< 0.001
Surgery								
Performed	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Unperformed	3.730 (2.988–4.657)	< .001	3.506 (2.479–4.959)	< .001	4.233 (2.717–6.596)	< 0.001	4.754 (3.120–7.244)	< 0.001
Chemotherapy								
Not received	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Received	1.050 (0.850–1.297)	0.654	1.436 (1.016–2.031)	0.041	1.507 (0.968–2.346)	0.069	0.598 (0.429–0.834)	0.002
Insurance status		0.211		0.898		0.139		0.099
Insuranced	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Unknown	1.162 (0.911–1.483)	0.227	0.914 (0.624–1.377)	0.642	1.208 (0.681–2.142)	0.518	1.392 (0.910–2.130)	0.127
Uninsuranced	1.495 (0.850–2.628)	0.163	0.970 (0.349–2.696)	0.954	4.202 (0.930–18.991)	0.062	1.990 (0.896–4.419)	0.091

Supplementary Table S2 lists the partial factors after the propensity score-matching process. The propensity matching process resulted in a balanced study population that included a chemotherapy group (n = 336) and a no chemotherapy group (n = 316). Kaplan-Meier curves of OS and cancer-specific survival (CCS) in the matched population, according to whether patients received chemotherapy in subgroups of grade × metastasis are represented in Fig. 2 and Supplementary Fig. S2. Patients were followed-up for a median of 29 months. In patients with G1 × M0, those who received chemotherapy had a worse overall survival ($P < 0.001$) and cancer-specific survival ($P < 0.001$). There was no statistically significant difference in OS and cancer-specific survival that favoured the chemotherapy group for patients with G1 × M1, G2 × M0 and G2 × M1. In the unmatched population, patients were followed-up for a median of 38 months (range, 0–143) and the mortality of pNETs as a whole did not exceed 50% (Supplementary Table S3).

4. Discussion

This study performed a population-based evaluation of secular trends in pNET incidence and identify associative factors. Moreover, we examined the impact of classic T/N/M staging and grading on OS, and determined that chemotherapy has a survival benefit for poorly differentiated and undifferentiated tumour grade population.

NETs appear to have an increasing incidence and the study of this unusual neoplasm is of increasing clinical relevance. It is clear that pNETs are biologically distinct from other NETs and are typically associated with specific genetic mutations linked to either the PI3Kinase/mTOR pathway (i.e., *PTEN*, *TSC*) or genes associated with epigenetic chromatin modelling (i.e., *DAXX/ATRX*, *MEN1*) [16]. In this population-based study, we found that the annual incidence of pNETs increased since 1973. We predicted the incidence rate will be over 2 per 100,000 both in males and females by 2025. There was an increasing percentage of early stage disease, especially with M0 status and well differentiation, as well as an increase in the incidence of patients with non-functioning pNETs, perhaps due to increased detection and disease recognition [17,18]. This finding is supported by a study from Massachusetts General Hospital that showed non-functioning and less-malignant pNETs may be an increasingly common entity [19]. Recent research has shown that using a combination of tumour markers chromogranin A and neuron-specific enolase as a laboratory evaluation not only has a high sensitivity, but can also predict prognosis and

A Modified Staging Classification for pNETs

Stage	G	T	N	M
IA	1	1	0	0
IB	1	2	0	0
IIA	1	1–2	1	0
	2	1–2	Any N	0
IIB	1–2	3–4	Any N	0
IIIA	1–2	Any T	Any N	1
IIIB	3–4	Any T	Any N	0
IV	3–4	Any T	Any N	1

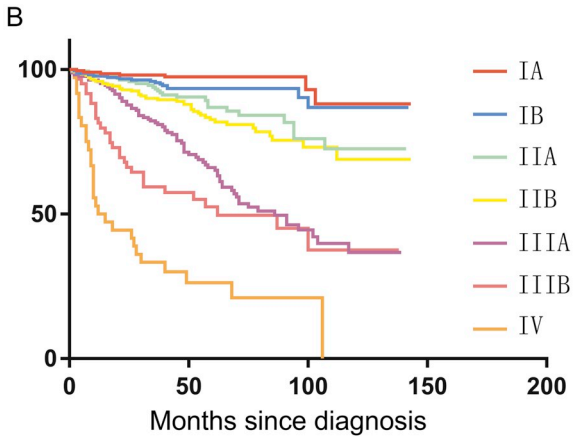

Fig. 1. (A) Modified staging classification for pNETs by G, T, N and M. Overall survival (B) of pNETs for the modified staging classification. P values for all adjacent stages are < 0.05. G, Grade; T, Tumour (Topography); N, Lymph Node; M, Metastasis.

treatment response [20–23]. Upon image inspection, the sensitivity of magnetic resonance imaging (MRI) ranges from 85 to 100% with a specificity of 75–100%. In a previous report, the use of registered positron emission tomography/computed tomography (PET/CT) images altered treatment decisions in 59.6% of patients compared to CT- or MRI-alone [24]. In addition, the steep rise in G1 pNETs is possibly related to the increased recognition and wide-spread adoption of the formalization of nomenclature, grading, and staging of these tumours. Unfortunately, although the increasing percentage of early stage disease was found, the proportion of pNET patients with extension (43.06%) or distant metastasis (37.87%) remains heavy in era 1 (Table 1). These data are similar to those obtained from several multicentre studies in that most patients with pNETs have regional or distant metastasis at diagnosis or during follow-up [25,26].

Although many studies have found an increasing incidence of pNETs, there is no widely acceptable staging system for this type of malignancy. According to the AJCC staging system, T/N/M stages showed very large 95% CIs for each stage, indicating lower predictive ability [27]. For the ENETS staging system, patients with stage I disease had a similar prognosis to patients with stage IIA disease, and the HR of death for patients with stage IIIB disease was even lower than that of patients with stage IIIA disease. Different modifications to staging pNETs have been proposed, but most of them have not considered T/N/M classification and tumour grading simultaneously. In our multivariate analysis, tumour grade and surgery were the most significant prognostic metrics. In the classification of tumour size, T2 and T3 had similar HRs. T status and N status was not associated with OS in certain subgroup analyses of grade. These findings may explain the poor performance of the classic staging criteria and strongly suggest a need for revising staging systems to include tumour grade. Therefore, we developed a modified staging system and applied it to pNETs in clinical practice. In our modified staging system, we reduced the influence of lymph nodes and tumour size on staging because of their low HRs. Survival curves were well-separated by stage using the modified system. These findings suggest that this staging classification is suitable for pNETs and can be adopted in clinical practice.

Compared with other types of NET, pNETs demonstrate a greater sensitivity and a higher response rate to chemotherapy. Evidence that the response rate increases with increasing grade has been previously reported [1,28]. In the ENETS consensus guidelines, chemotherapy is recommended for treating pNETs with distant metastases of any grade. The recommended chemotherapeutic regimen for G3 tumours is cisplatin and etoposide, and high response rates have been reported [1]. Historically, streptomycin-based regimens have been standard therapy for G1/G2 pNETs, but the toxicity of this regimen was significant, which limited its use [1,29]. It has also been reported that streptozocin is ineffective in patients with well-differentiated NETs [30]. We found a similar phenomenon in the univariate analysis, in that patients with G3/G4 pNETs benefited from chemotherapy, whether they had metastases (10.0 months *vs.* 2.0 months; $P < 0.001$) or did not (22.0 months *vs.* 2.0 months; $P = 0.005$). However, surgery has a higher HR than chemotherapy, which implies that surgery has a greater therapeutic effect. Chemotherapy was not associated with a survival benefit in patients with G1/G2 pNETs, for both metastatic and non-metastatic subgroups. It is worth pointing out that for patients with G1 and non-metastatic pNETs show the opposite result of curative effect after receiving chemotherapy (69.3 months *vs.* 110.1 months; $P < 0.001$). Some possible reasons for this finding includes high toxicity and a low response rate, but another explanation is that the confounding factors were not fully adjusted. Therefore, the role of chemotherapy for G3/G4 pNETs has been affirmed, whereas well-differentiated pNETs are not recommended for chemotherapy. Tumour grade should be a means of selecting patients for chemotherapy instead of M status.

However, our study design was limited. In terms of tumour staging, it has been proposed that for tumour size, 3 cm appears to be the optimal cut-off point to determine differences in survival [9]. Similarly, another series out of Johns Hopkins University found that Ki-67 expression rates have a linear relationship with mortality, calling into question the validity of stratifying Ki-67 rates into categories similar to grading systems [8]. Future studies are needed to provide more reasonable and concise classifications. The purpose of our modified staging criteria was to show the operability of the utility of including tumour grade. The staging of pNETs will likely continue to evolve in the coming years as our understanding increases. In terms of chemotherapy, a weakness of our analysis was the limited information regarding treatment regimens and the number of administered cycles, as well as the uncertainties regarding the completeness of the chemotherapy data. The chemotherapy data provided by SEER is limited to only whether the patient received chemotherapy treatment.

There has been a steady increase in the recognized incidence of pNETs, coincident with the migration to earlier T, N, and M stage and higher levels of differentiation. Owing to increased diagnoses, incidence will continue to rise. Grade was found to be superior to 'T', 'N', or 'M' status in predicting outcomes and selecting patients for chemotherapy. It is necessary and feasible to combine grade into current staging guidelines.

Provenance and peer review

Not commissioned, externally peer-reviewed.

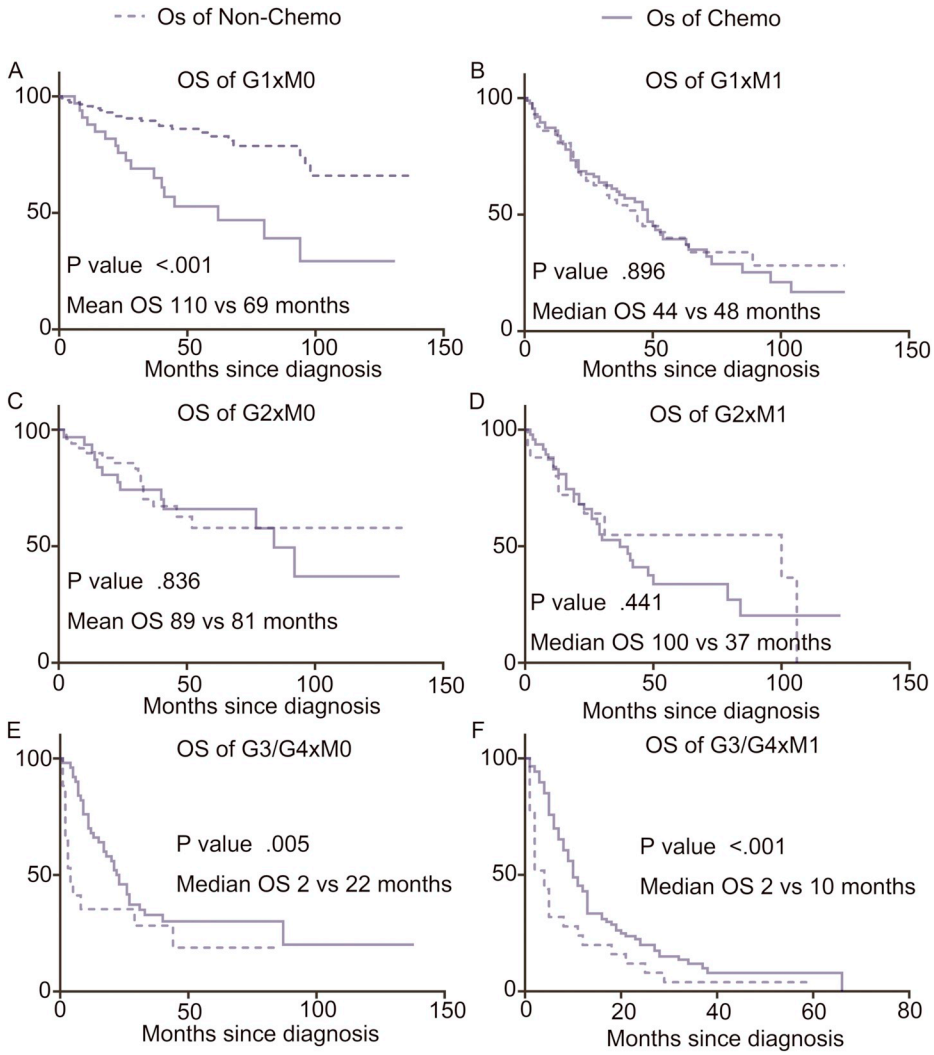

Fig. 2. Overall survival of G1M0 (A), G1M1 (B), G2M0 (C), G2M1 (D), G3/G4M0 (E), and G3/G3M1 (F) tumours. Kaplan-Meier estimates by tumour grade and M status for patients with or without chemotherapy after propensity score matching. M, Metastasis.

Data statement

All data were extracted from the SEER database.

Search formula:

{ Site and Morphology. Histologic Type ICD-0-3} = 8150.8240–8244.8246,8249].

0R ((Site and Morphology. Histologic Type ICD-0-3} = 8151–8157))

AND{ Site and Morphology. Site recode ICD-0-3/WHO 2008} = ' Pancreas'.

AND{ Other. Type of Reporting Source}! = ' Autopsy only, Death certificate only'.

AND{ Multiple Primary Fields. First malignant primary indicator} = Yes'.

Disclosure summary

The authors have nothing to disclose.

Ethical approval

The SEER Program collects data from population-based cancer registries with anonymous information. The SEER is a publicly available database and data extracted from SEER was deemed “non-human study” by the North Shore LIJ IRB committee.

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Conflicts of interest

No conflicts of interest.

Author contribution

Jie Yao conceived and designed this article. Huamin Zhai conducted the process associated with Qingbo Feng and Duguang Li, and all of them were first co-author s in this manuscript. Xiaowei Qian and Ling Li helped to guide and analyse the statistic data. All authors read and approved the final manuscript.

Research registration number

UIN:researchregistry4579.

Guarantor

Jie Yao is the guarantor of this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.03.006.

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