Survival Nomograms for Patients with Pancreatic Neuroendocrine Tumors: A Population-based Study

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Research

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Abstract

Background: Although pancreatic neuroendocrine tumors (PNETs) are considered indolent tumors, most patients are diagnosed at an advanced stage. We aimed to establish a nomogram for clinical use to predict the survival of PNET patients using the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: Based on the SEER database, 1,103 patients with PNETs were enrolled and randomly divided into training and validation sets. We performed Kaplan-Meier analysis and Cox proportional hazard regression analysis in the training set to evaluate the value of the prognostic factors. A nomogram was then constructed to analyze these independent prognostic factors for predicting the overall survival (OS) and specific cancer survival (CSS). C-index, calibration curve, and decision curve analysis were used to evaluate the predictive accuracy of the nomogram.

Results: Age, primary site, TNM stage, grade, and surgery were associated with OS and CSS in the multivariate models. Nomograms were established depending on these risk factors and had a better discrimination power than the TMN stage. The validation techniques showed that the nomograms were able to predict the 3- and 5-year OS and CSS accurately, and also proved to be superior.

Conclusions: Nomograms were established depending on these risk factors and had a better discrimination power than the TMN stage. The validation techniques showed that the nomograms were able to predict 3- and 5-year OS and CSS accurately, and also proved to be superior.

Introduction

Pancreatic neuroendocrine tumors (PNETs) are a relatively rare histological type of malignant pancreatic tumors, accounting for approximately 1%-3% of pancreatic neoplasms [1; 2]. Over the last two decades, the incidence of PNETs has increased due to improved diagnostic techniques, while the mortality has decreased due to the progress in understanding the pathophysiology and natural history of PNETs as well as better treatment and management [3]. Although PNETs are considered long-term indolent tumors, the outcomes of patients with PNETs are highly variable because of their high genetic heterogeneity [4], tissue histological differentiation, Ki-67 proliferation index, and tumor stage [5]. Thus, a personalized management strategy for PNET patients is urgently needed along with a relevant statistical predictive model [6].

Previously, the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TMN) staging system was broadly utilized to stratify the outcomes of patients with PNETs [7]. However, the accuracy and efficiency of the AJCC tumor staging system for patients with PNETs remain doubtful [8]. In recent years, several studies have demonstrated that additional risk factors, including age, sex, race, primary tumor site, and gene mutations, should be included in a novel prognostic indicator system for PNET patients [8, 9, 10, 11].

Nomograms, which are statistics-based methods, have been widely applied in prognosis-related clinical studies [12]. In addition, once the clinical variables are incorporated, the nomograms can specifically calculate the individual survival scores [13]. The Surveillance, Epidemiology, and End Results (SEER) database provides data on patient characteristics, including patient demographics, histological differentiation, primary tumor site, TMN stage at diagnosis, treatment, and follow-up for public use [14].

In this study, the SEER database was utilized to obtain relevant data, which was analyzed to identify possible independent prognostic factors in patients with PNETs. Depending on these prognostic factors, a novel nomogram was constructed and compared with the AJCC TMN system for predicting the overall survival (OS) and cancer specific survival (CSS).

Materials And Methods

Data acquisition and variables

The SEER database provides statistical data about cancer epidemiology and survival in the United States for public use. The SEER*Stat software (version 8.3.5) was used to extract the detailed clinicopathological information of patients with PNETs. The criteria for the included medical records in this study were as follows: Third Edition (ICD-O-3), histology codes 8246/3. Patients were excluded if the race, primary site, grade, T stage, N stage, M stage, explicit distant organ metastasis, number of months of survival were unknown, or if the clinicopathological information including TMN stage and therapy was incomplete.

In order to construct and validate the nomograms, all enrolled patients were randomly divided in a ratio of 3:1 into a training set and a validation set. Institutional review board approval was not necessary for this study owing to the publicly available nature of the SEER program, and we obtained permission from SEER to access the research data (accession number: 15502-Nov2019).

For each patient, the following variables were acquired: age of diagnosis (transformed into the classification variable, < 60 y and ≥ 60 y), sex (male, female), race record (White, Black, others), primary tumor site (head, body, tail, others), histological differentiation grade (I, II, III, IV), 7th AJCC TMN stage, T stage (T1, T2, T3, T4), N stage (N0, N1), M stage (M0, M1), bone metastasis, brain metastasis, liver metastasis, surgical treatment, follow-up information, and cause of death. The cutoff for follow-up was December, 2015. The endpoints were OS and CSS. OS was the primary endpoint, indicating the percentage of people in the study or treatment group who were alive for a given period of time after the diagnosis. CSS was the secondary endpoint, indicating the time period from diagnosis to death due to PNET or censoring.

Statistical analysis

The Chi-squared test was employed to compare the distribution differences between the variables in the training and validation sets. Univariate and multivariate Cox regression analyses were used to identify the possible independent prognostic factors for predicting OS and CSS. Nomograms were established based on the results of the multivariate analysis.

The efficiency of nomograms was measured using a discrimination and calibration curve. The discrimination was evaluated with the concordance index (C-Index); a higher C-index suggests a better prediction ability to separate patients with different prognoses. A calibration plot was utilized to depict the difference between the outcome predicted by the nomograms and the actual outcome. The 45-degree line in a calibration plot is considered as a perfect model to compare the actual prognoses. Receiver operating characteristic curve (ROC) analysis was employed to measure sensitivity and specificity. Additionally, we compared the nomograms with the 7th edition AJCC TNM staging system using the C-index with the t-test. Furthermore, decision curve analysis (DCA) was used to visualize the threshold probability ranges for comparison between the AJCC TNM staging system and nomograms. Statistical analyses were performed using SPSS software (version 26.0) and R software (version 4.0.2) with RMS and survival packages.

Results

Patients characteristics

A total of 1,103 eligible patients with PNETs diagnosed between 2010 and 2015 were enrolled in the study. The clinicopathological characteristics are shown in Table 1. Among them, 775 patients were assigned to the training set and 328 were assigned to the validation set. Regarding age, the majority of the patients were ≥ 60 years (55.2%) . Of the total eligible patients, 617 (55.9%) were men and 486 (44.1%) were women. The most common tumor site was the tail of the pancreas (39.2%), followed by the head of the pancreas (34.0%), body of the pancreas (15.8%) and other sites in the pancreas (11.1%). Patients with histologically well-differentiated tumors accounted for 53.7%. A total of ~77.2% patients underwent surgery, 36.4% had T1 stage, 65.7% had N0, and 73.3% had M0. A small proportion of the patients had distant metastases, which included bone metastasis (2.2%), brain metastasis (0.4%), liver metastasis (23.8%), and lung metastasis (2.4%) (Table 1).

Table 1
Patient Demographics and Pathological Characteristics

	All patients <i>n</i> (%)	Training set <i>n</i> (%)	Validation set <i>n</i> (%)	<i>P</i> - value ^{<i>n</i>}
Total	1103(100)	775(70.3)	328(29.7)	
Age				0.339
< 60	494(44.8)	336(30.5)	158(14.3)	
≥60	609(55.2)	439(39.8)	170(15.4)	
Sex				0.611
Male	617(55.9)	441(40.0)	176(16.0)	
Female	486(44.1)	334(30.3)	152(13.8)	
Race				0.761
White	869(78.8)	603(54.7)	266(24.1)	
Black	109(9.9)	78(7.1)	31(2.8)	
Others ^a	125(11.3)	94(8.5)	31(2.8)	
Primary Site				0.980
Head of pancreas	375(34.0)	270(24.5)	105(9.5)	
Body of pancreas	174(15.8)	119(10.8)	55(5.0)	
Tail of pancreas	432(39.2)	299(27.1)	133(12.1)	
Other parts of pancreas ^b	122(11.1)	87(7.9)	35(3.2)	
Grade				0.991
Well differentiated; Grade I	717(65.0)	501(45.4)	216(19.6)	
Moderately differentiated; Grade II	193(17.5)	138(12.5)	55(5.0)	
Poorly differentiated; Grade III	145(13.1)	100(9.1)	45(4.1)	
Undifferentiated; anaplastic; Grade IV	48(4.4)	36(3.3)	12(1.1)	
AJCC Stage				0.960
I	470(42.6)	337(30.6)	133(12.1)	

Notes: ^a other race include American Indian/Alaska Native, Asian or Pacific Islander. ^b other primary site include overlapping lesion of pancreas, islets of Langerhans, other specified parts of pancreas and pancreas(NOS).

	All patients <i>n</i> (%)	Training set <i>n</i> (%)	Validation set <i>n</i> (%)	<i>P</i> - value ^a
II	306(27.7)	215(19.5)	91(8.3)	
III	33(3.0)	21(1.9)	12(1.1)	
IV	294(26.7)	202(18.3)	92(8.3)	
AJCC T				0.141
T1	291(26.4)	198(18.0)	93(8.4)	
T2	372(33.7)	272(24.7)	100(9.1)	
T3	363(32.9)	258(23.4)	105(9.5)	
T4	77(7.0)	37(3.4)	30(2.8)	
AJCC N				0.412
N0	725(65.7)	519(47.1)	206(18.7)	
N1	378(34.3)	256(23.2)	122(11.1)	
AJCC M				0.793
M0	809(73.3)	573(51.9)	236(21.4)	
M1	294(26.7)	202(18.3)	92(8.3)	
Bone metastasis				0.219
Yes	24(2.2)	13(1.2)	11(1.0)	
No	1079(97.8)	762(69.1)	317(29.6)	
Brain metastasis				0.979
Yes	4(0.4)	3(0.3)	1(0.1)	
No	1099(99.6)	772(70.0)	327(29.6)	
Liver metastasis				0.949
Yes	262(23.8)	182(16.5)	80(7.3)	
No	841(76.2)	593(53.8)	248(22.5)	
Lung metastasis				0.859
Yes	26(2.4)	17(1.5)	9(0.8)	

Notes: ^a other race include American Indian/Alaska Native, Asian or Pacific Islander. ^b other primary site include overlapping lesion of pancreas, islets of Langerhans, other specified parts of pancreas and pancreas(NOS).

	All patients <i>n</i> (%)	Training set <i>n</i> (%)	Validation set <i>n</i> (%)	<i>P</i> - value ^{<i>n</i>}
No	1077(97.6)	758(68.7)	319(28.9)	0.816
Surgery				
Surgery performed	851(77.2)	602(54.6)	249(22.6)	
No Surgery	252(22.8)	173(15.7)	79(7.2)	
Notes: ^a other race include American Indian/Alaska Native, Asian or Pacific Islander. ^b other primary site include overlapping lesion of pancreas, islets of Langerhans, other specified parts of pancreas and pancreas(NOS).				

Independent prognostic factors for OS and CSS

As shown in Table 2 and Table 3, age, primary site, histological differentiation grade, AJCC stage, T stage, N stage, M stage, bone metastasis, brain metastasis, liver metastasis, lung metastasis, and surgery were significantly associated with OS and CSS on univariate analysis with Kaplan-Meier survival analysis in the training set. We further utilized the significant risk factors from the results of the univariate analysis to perform multivariate Cox regression analysis. The results revealed that age, primary site, histological differentiation grade, AJCC stage, and surgery were the independent risk factors for OS and CSS. The establishment of the nomograms of 3- and 5-year OS (**Fig. 1a**) and CSS (**Fig. 1b**) were based on these significant independent prognostic variables. Each independent prognostic factor was assigned a specific score based on its risk ratio. The nomograms showed that the TNM stage had the greatest influence on prognosis, followed by histological differentiation, surgery, age, and tumor site. By adding the scores for each selected variable, it is possible to calculate the likelihood of survival for an individual patient.

Table 2
Univariate and Multivariate Analyses of Overall Survival in the Training Set

Variables	Univariate analysis P-value	Multivariate analysis HR(95%CI)	P-value
Age	< 0.001*		
< 60		Reference	
≥60		1.63(1.16–2.27)	0.005*
Sex	0.522		
Male			
Female			
Race	0.610		
White			
Black			
Others ^a			
Primary Site	< 0.0001*		
Head of pancreas		Reference	
Body of pancreas		0.72(0.43–1.21)	0.225
Tail of pancreas		0.63(0.44–0.91)	0.014*
Other parts of pancreas ^b		0.70(0.41–1.19)	0.185
Grade	< 0.0001*		
Well differentiated; Grade I		Reference	
Moderately differentiated; Grade II		1.16(0.74–1.83)	0.509
Poorly differentiated; Grade III		3.74(2.25–5.55)	< 0.001*
Undifferentiated; anaplastic; Grade IV		4.49(2.68–7.54)	< 0.001*
AJCC Stage	< 0.0001*		
I		Reference	

Notes: ^a other race include American Indian/Alaska Native, Asian or Pacific Islander. ^b other primary site include overlapping lesion of pancreas, islets of Langerhans, other specified parts of pancreas and pancreas(NOS).

Variables	Univariate analysis P-value	Multivariate analysis HR(95%CI)	P-value
II		1.97(0.60–6.45)	0.004*
III		4.61(1.62–13.13)	0.004*
IV		12.19(4.30-34.55)	0.001*
AJCC T	< 0.0001*		
T1		Reference	
T2		1.04(0.49–2.23)	0.917
T3		1.22(0.55–2.70)	0.617
T4		0.86(0.34–2.19)	0.758
AJCC N	< 0.0001*		
N0		Reference	
N1		1.23(0.89–1.73)	0.210
AJCC M	< 0.0001*	-	
M0		-	
M1			
Bone metastasis	< 0.0001*		
Yes		Reference	
No		0.63(0.28–1.43)	0.270
Brain metastasis	< 0.0001*		
Yes		Reference	
No		0.39(0.09–1.74)	0.218
Liver metastasis	< 0.0001*		
Yes		Reference	
No		0.73(0.38–1.38)	0.330

Notes: ^a other race include American Indian/Alaska Native, Asian or Pacific Islander. ^b other primary site include overlapping lesion of pancreas, islets of Langerhans, other specified parts of pancreas and pancreas(NOS).

Variables	Univariate analysis P-value	Multivariate analysis HR(95%CI)	P-value
Lung metastasis	< 0.0001*		
Yes		Reference	
No		1.02(0.52-2.00)	0.950
Surgery	< 0.0001*		
Surgery performed		Reference	
No Surgery		4.14(2.86–6.01)	< 0.0001*
Notes: ^a other race include American Indian/Alaska Native, Asian or Pacific Islander. ^b other primary site include overlapping lesion of pancreas, islets of Langerhans, other specified parts of pancreas and pancreas(NOS).			

Table 3
Univariate and Multivariate Analyses of Cancer specific Survival in the Training Set

Variables	Univariate analysis P-value	Multivariate analysis HR(95%CI)	P-value
Age	< 0.001*		
< 60		Reference	
≥60		1.65(1.18–2.32)	0.004*
Sex	0.463		
Male			
Female			
Race	0.634		
White			
Black			
Others ^a			
Primary Site	< 0.0001*		
Head of pancreas		Reference	
Body of pancreas		0.75(0.45–1.25)	0.265
Tail of pancreas		0.63(0.44–0.91)	0.014*
Other parts of pancreas ^b		0.72(0.42–1.22)	0.217
Grade	< 0.0001*		
Well differentiated; Grade I		Reference	
Moderately differentiated; Grade II		1.21(0.77–1.90)	0.415
Poorly differentiated; Grade III		3.81(2.56–5.67)	< 0.001*
Undifferentiated; anaplastic; Grade IV		4.39(2.60–7.43)	< 0.001*
AJCC Stage	< 0.0001*		
I		Reference	
II		3.02(1.38–6.61)	0.006*

Notes: ^a other race include American Indian/Alaska Native, Asian or Pacific Islander. ^b other primary site include overlapping lesion of pancreas, islets of Langerhans, other specified parts of pancreas and pancreas(NOS).

Variables	Univariate analysis P-value	Multivariate analysis HR(95%CI)	P-value
III		4.93(1.63–14.91)	0.005*
IV		4.98(1.88–13.17)	0.001*
AJCC T	< 0.0001*		
T1		Reference	
T2		1.03(0.48–2.20)	0.948
T3		1.20(0.55–2.67)	0.641
T4		0.88(0.34–2.22)	0.780
AJCC N	< 0.0001*		
N0		Reference	
N1		1.23(0.87–1.72)	0.237
AJCC M	< 0.0001*	-	
M0		-	
M1			
Bone metastasis	< 0.0001*		
Yes		Reference	
No		0.63(0.28–1.43)	0.272
Brain metastasis	< 0.0001*		
Yes		0.28(0.09–1.71)	
No			0.209
Liver metastasis	< 0.0001*		
Yes		Reference	
No		0.74(0.39–1.40)	0.349
Lung metastasis	< 0.0001*		
Yes		Reference	
No		1.03(0.53–2.03)	0.921

Notes: ^a other race include American Indian/Alaska Native, Asian or Pacific Islander. ^b other primary site include overlapping lesion of pancreas, islets of Langerhans, other specified parts of pancreas and pancreas(NOS).

Variables	Univariate analysis P-value	Multivariate analysis HR(95%CI)	P-value
Surgery	< 0.0001*		
Surgery performed		Reference	
No Surgery		3.98(2.74–5.79)	< 0.0001*
Notes: ^a other race include American Indian/Alaska Native, Asian or Pacific Islander. ^b other primary site include overlapping lesion of pancreas, islets of Langerhans, other specified parts of pancreas and pancreas(NOS).			

Validation of nomograms

The discriminating ability of the nomograms was evaluated by C-index values, calibration curves, time-dependent ROC curves, and decision curve analysis. A higher C-index value indicates a more favorable predictive ability. The OS predicting nomogram had a C-index of 0.869 (95% confidence intervals [CI]: 0.843-0.897) in the training cohort and 0.852 (95% CI: 0.806-0.898) in the validation cohort. The predictive nomogram for CSS demonstrated a C-index of 0.870 (95% CI: 0.843-0.898) and 0.855 (95% CI: 0.808-0.901) in the training set and validation set, respectively. Moreover, absence of obvious deviations from the reference line in the calibration curves indicated excellent consistency and acceptance consistency between the model prediction and actual observation values for the 3- and 5- OS and CSS (Figure 2 and Figure 3). ROC analysis was used to evaluate the sensitivity and specificity of the predictive models. The area under the curve (AUC) values of the 3- and 5- year OS were 0.918 and 0.902 in the training cohort (**Fig. 2a** and **Fig. 2b**), 0.905 and 0.872 in the validation cohort (**Fig. 2c** and **Fig. 2d**), respectively. Meanwhile, the AUC values of the 3- and 5- year CSS were 0.919 and 0.903 in the training cohort (**Fig. 3a** and **Fig. 3b**), 0.904 and 0.893 in the validation cohort (**Fig. 3c** and **Fig. 3d**), respectively. Furthermore, DCA analysis was utilized to visually illustrate the clinical applicability and superiority of the nomograms for OS and CSS over TNM staging (**Fig. 5**). Moreover, we also compared the C-index values between the nomograms and TNM staging both in the training and validation sets for OS and CSS with the t test, which are shown in Table 4.

Table 4
Comparison of C-indexes between the nomograms, TNM, in PNETs patients

		Training set			Validation set		
		HR	95%CI	<i>P</i> -value	HR	95%CI	<i>P</i> -value
OS	Nomogram	0.869	0.843–0.897		0.852	0.806–0.898	
	TNM 7th stage	0.790	0.761–0.820	< 0.0001	0.764	0.716–0.811	< 0.01
CSS	Nomogram	0.870	0.843–0.898		0.855	0.808–0.901	
	TNM 7th stage	0.791	0.762–0.821	< 0.0001	0.762	0.715–0.810	< 0.01

Discussion

Although PNETs account for a small proportion of pancreatic malignancies, their annual incidence has been steadily rising [15]. More importantly, PNETs are highly heterogeneous tumors that exhibit varying biological behaviors [16]. Using traditional staging systems alone to assess the prognosis is inaccurate and impersonalized. This study used the SEER program to establish the OS and CSS prognosis in patients with PNETs, which demonstrated a better identification and calibration ability, as well as a comparable prediction ability compared to the traditional AJCC TNM staging system. In fact, the clinical values of age, race, histological differentiation grade, TNM stage, and surgery in patients with PNETs were emphasized in the nomograms, which can promote the popularization of patient counseling and personalized treatment. The hazard ratio (HR) of PNETs increased with age, and the survival rate was worse in patients over 60 years than in younger patients. Compared with a high histological differentiation grade and advanced TNM stage, patients with early PNETs had a more optimistic outcome. Surgical treatment is always recommended for patients with PNETs with or without distant metastasis. Similar to pancreatic ductal adenocarcinoma [17], patients with tumors located in the tail or body of the pancreas have a more favorable outcome.

Furthermore, race, sex, T stage, N stage, M stage, specific distant organ metastases comprising brain, bone, liver, and lung metastasis, were not independent prognostic variables associated with OS and CSS in patients with PNETs in the present study. Although all the above variables have been considered as significant factors influencing the treatment before, few intensive studies with a large population of PNETs patients have been carried out to confirm this.

To date, nomograms have provided reasonable, repeatable, and rigorous algorithms, graphical presentations, and statistical tools for individualized prognostic evaluation. The comprising parameters should be easily acquired and measurable. Compared with a single stage prognostic factor in the DCA curve, comprehensive nomograms with absolute net benefit advantage provide excellent clinical application value. Nomograms can predict OS and CSS with high accuracy, sensitivity, and specificity, which can ensure effective clinical application.

Although several studies have demonstrated that nomograms could be ideal statistical prediction models for PNETs [18, 19, 20], our updated nomograms were established with more detailed clinical information after excluding indeterminacy parameters from the SEER database. This makes our predictive models more accurate and simple. Additionally, the nomograms in this study could not only predict the OS, but also predict the CSS. It improved the utility of nomograms for clinical applications compared with a previous study [21].

This study has several limitations. First, we used retrospective data, which has an inherent selection bias. Second, some important parameters associated with prognosis could not be obtained, which resulted in an imperfect model. Third, the TNM staging classification in the SEER database was still according to the AJCC 7th edition, although the AJCC 8th edition has been updated in 2017. The database did not provide certain details, such as tumor recurrence and subsequent metastasis after the first surgery. Finally, an external validation study should be used to evaluate the model.

We established and verified a novel nomogram model for a more accurate 3- and 5- OS and CSS prediction for individual patients with PNETs based on a large, population-based cohort, which showed a good performance in both the training and validation sets. However, more detailed clinicopathology studies are needed in the future.

Declarations

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Ethics approval and consent to participate

All the clinical data were downloaded from the public database SEER according to relevant user guidelines. Therefore, it can be ascertained that all patients provided written informed consent.

Patients consent for publication

Not applicable.

Data availability statement

Publicly available datasets were analyzed in this study, these can be found in Surveillance, Epidemiology, and End Results (SEER) database (<https://seer.cancer.gov/seerstat/>), which are open to the public under some guidelines. Therefore, it is confirmed that all written informed consent was obtained. The data analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

The study conception and design were performed by Chaohao Huang. Material preparation, data collection, and analysis were performed by Bi Lin, Dinglai Yu, Shengchuan Chen, and Daojie Wang. The first draft of the manuscript was written by Chaohao Huang. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors have no conflicts of interest to declare.

References

- [1] J. Hallet, C.H. Law, M. Cukier, R. Saskin, N. Liu, and S. Singh, Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer* 121 (2015) 589-97.
- [2] L. Khanna, S.R. Prasad, A. Sunnapwar, S. Kondapaneni, A. Dasyam, V.S. Tammisetti, U. Salman, A. Nazarullah, and V.S. Katabathina, Pancreatic Neuroendocrine Neoplasms: 2020 Update on Pathologic and Imaging Findings and Classification. *Radiographics* 40 (2020) 1240-1262.
- [3] S. Gaujoux, and F. Menegaux, Going Above and Beyond the Pancreatic Neuroendocrine Tumor Classification. *JCO Oncol Pract* (2020) OP2000809.
- [4] X. Tang, Y. Shao, X. Yi, P.J. Newey, D. Li, K. Ding, and G. and Gastrointestinal Cancer Evolution Study, Metastatic Timing and Genetic Heterogeneity in the Evolution of a Pancreatic Neuroendocrine Tumor. *Am J Gastroenterol* (2020).

- [5] S. Kalantri, P. Bakshi, and K. Verma, Grading of pancreatic neuroendocrine tumors on endoscopic ultrasound-guided fine-needle aspiration using Ki-67 index and 2017 World Health Organization criteria: An analysis of 32 cases. *Cytojournal* 17 (2020) 21.
- [6] S. Partelli, M. Mazza, V. Andreasi, F. Muffatti, S. Crippa, D. Tamburrino, and M. Falconi, Management of small asymptomatic nonfunctioning pancreatic neuroendocrine tumors: Limitations to apply guidelines into real life. *Surgery* 166 (2019) 157-163.
- [7] H. Wang, Z. Lin, G. Li, D. Zhang, D. Yu, Q. Lin, J. Wang, Y. Zhao, G. Pi, and T. Zhang, Validation and modification of staging Systems for Poorly Differentiated Pancreatic Neuroendocrine Carcinoma. *BMC Cancer* 20 (2020) 188.
- [8] Z. Wang, W. Jiang, L. Zheng, J. Yan, J. Dai, C. Huang, Q. Zhang, Z. Yin, X. Gong, and Y. Zhang, Consideration of Age Is Necessary for Increasing the Accuracy of the AJCC TNM Staging System of Pancreatic Neuroendocrine Tumors. *Front Oncol* 9 (2019) 906.
- [9] A. Puccini, K. Poorman, M.E. Salem, D. Soldato, A. Seeber, R.M. Goldberg, A.F. Shields, J. Xiu, F. Battaglin, M.D. Berger, R. Tokunaga, M. Naseem, A. Barzi, S. Iqbal, W. Zhang, S. Soni, J.J. Hwang, P.A. Philip, S. Sciallero, W.M. Korn, J.L. Marshall, and H.J. Lenz, Comprehensive Genomic Profiling of Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NENs). *Clin Cancer Res* (2020).
- [10] G. Muscogiuri, B. Altieri, M. Albertelli, A. Dotto, R. Modica, L. Barrea, G. Fanciulli, T. Feola, R. Baldelli, R.M. Ruggeri, M. Gallo, V. Guarnotta, P. Malandrino, E. Messina, M.A. Venneri, E. Giannetta, D. Ferone, A. Colao, A. Faggiano, and N. group, Epidemiology of pancreatic neuroendocrine neoplasms: a gender perspective. *Endocrine* 69 (2020) 441-450.
- [11] D.K. DePalo, R.M. Lee, A.G. Lopez-Aguilar, A.C. Gamboa, F. Rocha, G. Poultsides, M. Dillhoff, R.C. Fields, K. Idrees, H. Nathan, D. Abbott, S.K. Maithel, M.C. Russell, and G. other members of the United States Neuroendocrine Tumor Study, Interaction of race and pathology for neuroendocrine tumors: Epidemiology, natural history, or racial disparity? *J Surg Oncol* 120 (2019) 919-925.
- [12] Y. Lin, M. Wang, J. Jia, W. Wan, T. Wang, W. Yang, C. Li, X. Chen, H. Cao, P. Zhang, and K. Tao, Development and validation of a prognostic nomogram to predict recurrence in high-risk gastrointestinal stromal tumour: A retrospective analysis of two independent cohorts. *EBioMedicine* 60 (2020) 103016.
- [13] D. Zhang, S. Yang, Y. Li, J. Yao, J. Ruan, Y. Zheng, Y. Deng, N. Li, B. Wei, Y. Wu, Z. Zhai, J. Lyu, and Z. Dai, Prediction of Overall Survival Among Female Patients With Breast Cancer Using a Prognostic Signature Based on 8 DNA Repair-Related Genes. *JAMA Netw Open* 3 (2020) e2014622.
- [14] K.M. Doll, A. Rademaker, and J.A. Sosa, Practical Guide to Surgical Data Sets: Surveillance, Epidemiology, and End Results (SEER) Database. *JAMA Surg* 153 (2018) 588-589.

- [15] A. Dasari, C. Shen, D. Halperin, B. Zhao, S. Zhou, Y. Xu, T. Shih, and J.C. Yao, Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol* 3 (2017) 1335-1342.
- [16] G. Perri, L.R. Prakash, and M.H.G. Katz, Pancreatic neuroendocrine tumors. *Curr Opin Gastroenterol* 35 (2019) 468-477.
- [17] Y. Zhang, L. Shang, P.P. Zhang, L.H. Chen, W. Wang, C. Fang, M. Qiu, X.Y. Feng, L. Zhou, M. Zhang, H.Y. Tan, X.D. Qiu, H. Wang, R. Lin, Q. Zhang, Y.J. Zeng, K.Z. Jin, X.J. Yu, L. Shen, M.H. Chen, J. Li, L.P. Li, and J. Chen, Clinicopathological features and prognostic validity of the European Neuroendocrine Tumor Society (ENETS) and American Joint Committee on Cancer (AJCC) 8th staging systems in colonic neuroendocrine neoplasms. *Cancer Med* 8 (2019) 5000-5011.
- [18] Z. Lin, H. Wang, Y. Zhang, G. Li, G. Pi, X. Yu, Y. Chen, K. Jin, L. Chen, S. Yang, Y. Zhu, G. Wu, J. Chen, and T. Zhang, Development and Validation of a Prognostic Nomogram to Guide Decision-Making for High-Grade Digestive Neuroendocrine Neoplasms. *Oncologist* 25 (2020) e659-e667.
- [19] A. Pulvirenti, A.A. Javed, L. Landoni, N.B. Jamieson, J.F. Chou, M. Miotto, J. He, M. Gonen, A. Pea, L.H. Tang, C. Nesi, S. Cingarlini, M.I. D'Angelica, A.J. Gill, T.P. Kingham, A. Scarpa, M.J. Weiss, V.P. Balachandran, J.S. Samra, J.L. Cameron, W.R. Jarnagin, R. Salvia, C.L. Wolfgang, P.J. Allen, and C. Bassi, Multi-institutional Development and External Validation of a Nomogram to Predict Recurrence After Curative Resection of Pancreatic Neuroendocrine Tumors. *Ann Surg* (2019).
- [20] C.G. Genc, A.P. Jilesen, S. Partelli, M. Falconi, F. Muffatti, F.J. van Kemenade, S. van Eeden, J. Verheij, S. van Dieren, C.H.J. van Eijck, and E.J.M. Nieveen van Dijkum, A New Scoring System to Predict Recurrent Disease in Grade 1 and 2 Nonfunctional Pancreatic Neuroendocrine Tumors. *Ann Surg* 267 (2018) 1148-1154.
- [21] D.L. Miao, W. Song, J. Qian, Z.G. Zhu, Q. Wu, C.G. Lv, and L. Chen, Development and Validation of a Nomogram for Predicting Overall Survival in Pancreatic Neuroendocrine Tumors. *Transl Oncol* 11 (2018) 1097-1103.

Figures

Figure 1

Nomograms for PNETs patients (A) Nomograms for 3- and 5-year-associated OS. (B) Nomograms for 3- and 5-year-associated CSS.

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Figure 2

Calibration plots of the training and validation sets for the OS-associated nomograms (A,B) The calibration plots of the training set in 3- and 5-year OS. (C,D) The calibration plots of the validation set in 3- and 5-year OS.

Figure 2

Calibration plots of the training and validation sets for the OS-associated nomograms (A,B) The calibration plots of the training set in 3- and 5-year OS. (C,D) The calibration plots of the validation set in 3- and 5-year OS.

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Calibration plots of the training and validation sets for the OS-associated nomograms (A,B) The calibration plots of the training set in 3- and 5-year OS. (C,D) The calibration plots of the validation set in 3- and 5-year OS.

Figure 3

Calibration plots of the training and validation sets for the CSS-associated nomograms (A,B) The calibration plots of the training set in 3- and 5-year CSS. (C,D) The calibration plots of the validation set in 3- and 5-year CSS.

Figure 3

Calibration plots of the training and validation sets for the CSS-associated nomograms (A,B) The calibration plots of the training set in 3- and 5-year CSS. (C,D) The calibration plots of the validation set in 3- and 5-year CSS.

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Calibration plots of the training and validation sets for the CSS-associated nomograms (A,B) The calibration plots of the training set in 3- and 5-year CSS. (C,D) The calibration plots of the validation set in 3- and 5-year CSS.

Figure 4

ROC analysis for training and validation sets (A) The ROC of 3 years OS for training set; (B) the ROC of 5 years OS for training set; (C) the ROC of 3 years OS for validation set; (D) the ROC of 5 years OS for validation set; (E) the ROC of 3 years CSS for training set; (F) the ROC of 5 years CSS for training set; (G) the ROC of 3 years CSS for validation set; and (H) the ROC of 5 years CSS for validation set.

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Figure 5

DCA of the training and validation sets for the CSS- and OS-associated nomograms (A,B) The DCA of nomogram in training set for OS (A) and CSS (B). (C,D) The DCA of nomogram in validation

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