

ORIGINAL ARTICLE

Using a Nomogram to Preoperatively Predict Distant Metastasis of Pancreatic Neuroendocrine Tumor in Elderly Patients

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Objective To establish a nomogram for predicting the distant metastasis risk of pancreatic neuroendocrine tumors (pNETs) in elderly patients.

Methods We extracted data of patients with diagnosis of pNETs at age ≥ 65 years old between 1973 and 2015 from the Surveillance, Epidemiology, and End Results (SEER) database. All eligible patients were divided randomly into a training cohort and validation cohort. Uni- and multivariate logistic regression analyses were performed on the training cohort to identify independent factors for distant metastasis. A nomogram was developed based on the independent risk factors using rms packages of R software, and was validated internally by the training cohort and externally by the validation cohort using C-index and calibration curves.

Results A total of 411 elderly patients were identified, of which 260 were assigned to training cohort and 151 to validation cohort. Univariate and multivariate logistic regression analyses indicated the tumor site (body/tail of pancreas: odds ratio [OR]=2.282; 95% confidence interval [CI]: 1.174 – 4.436, $P<0.05$), histological grade (poorly differentiated/undifferentiated: OR=2.600, 95% CI: 1.266–5.339, $P<0.05$), T stage (T2: OR=8.913, 95% CI: 1.985–40.010, $P<0.05$; T3: OR=11.830, 95% CI: 2.530–55.350, $P<0.05$; T4: OR=68.650, 95% CI: 8.020–587.600, $P<0.05$), and N stage (N1: OR=3.480, 95% CI: 1.807–6.703, $P<0.05$) were identified as independent risk factors for distant metastasis of pNETs in elderly. The nomogram exhibited good predicting accuracy, with a C-index of 0.809 (95% CI: 0.757 – 0.861) in internal validation and 0.795 (95% CI: 0.723 – 0.867) in external validation, respectively. The predicted distant metastasis rates were in satisfactory agreement with the observed values by the calibration curves.

Conclusion The nomogram we established showed high discriminative ability and accuracy in evaluation of distant metastasis risk in elderly pNETs patients, and could provide a reference for individualized tumor evaluation and treatment decision in elderly pNETs patients.

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INTRODUCTION

PANCREATIC neuroendocrine tumors (pNETs) are a group of low-incidence highly heterogeneous malignant tumors originating from pancreas. The incidence of pNETs has gradually increased in recent years.^[1-3] Most pNETs grow slowly and have low invasiveness. Compared with other malignant tumors, patients with pNETs may achieve a relatively long survival time.^[1] Unfortunately, pNETs are prone to distant metastasis.^[1, 3] About 50% – 60% pNETs patients have distant metastasis upon initial diagnosis as reported. Throughout the course of the disease, the probability of distant metastasis is as high as 80%.^[3-5] Once distant metastasis occurs, the survival time of pNETs patient is greatly shortened. The 5-year survival rate of pNETs patients with distant metastasis is 13%–54%, compared to 75%–99% of those without distant metastasis.^[6] Identification of risk factors for distant metastasis in patients with pNETs is helpful for assessment of the stage and prognosis.

In recent years, societal aging has become an increasingly important issue; meanwhile, the proportion of elderly patients with cancer in population has gradually increased.^[7-9] Physiological and psychological state of elderly cancer patients are different from young cancer patients;^[8] moreover, the immune system of elderly is usually deficient, which may weaken the inhibition of tumor.

In the Surveillance, Epidemiology, and End Results (SEER) database, over 50% (1743/3431) of pNETs patients with age ≥ 65 years old had distant metastasis. It is of great significance to identify the factors associated with distant metastasis and to predict the risk of metastasis in elderly pNETs patients, which has been poorly defined by far.

Nomogram model method integrates multiple indices to predict the probability of a certain resulting event individually and accurately. In the current study, we investigate the risk factors for distant metastasis in pNETs patients ≥ 65 years old with regression analyses, and subsequently construct a nomogram to predict the risk of distant metastasis with performance validations based on the data from SEER database.

MATERIALS AND METHODS

Data source and patient selection

The SEER database^[10] was accessed using SEER* Stat

software (version 8.3.5).^[11] We retrieved data of patients with pNETs from 1973 to 2015. The pNETs was defined by the International Classification of Diseases for Oncology third edition (ICD-O3) codes as follows: 8150/3, 8151/3, 8152/3, 8153/3, 8155/3, 8156/3, 8240/2, 8240/3, 8241/3, 8242/3, 8243/3, 8246/2, 8246/3, and 8249/3. Anatomical sites of the tumor in pancreas were included (C25.0-C25.9). Patients with two or more tumors were excluded.

Data filtering, collection, and outcome measurement

The variables of age at diagnosis, sex, race, year of diagnosis, site of the tumor in pancreas, histological grade, T stage (6th edition), N stage (6th edition), M stage, and marital status were retrieved. We carefully screened all retrieved data. Patients was regarded as illegible and excluded from the study if any of following data items was missing, including clinical stage, histological grade, T stage, N stage, marital status, site of tumor in pancreas, and metastasis status at diagnosis. The identified patients were divided into a training set and validation set by random number table method. The primary outcome was distant metastasis of pNETs.

Univariate and multivariate logistic regression

With data of the training set, we used univariate logistic regression model to analyze risk factors for distant metastasis. Variables with $P < 0.1$ were further analyzed using multivariate logistic regression model. Univariate and multivariate logistic proportional analyses were performed using IBM SPSS Statistics (version 22.0; Chicago, IL, USA). P values were two-sided and <0.05 was regarded as statistically significant.

Construction of nomogram

A nomogram for predicting the risk of distant metastasis of pNETs in elderly patients was constructed by integrating all independent risk factors based on the results of the multivariate logistic analysis. The rms package in R 3.6.1 software^[12] was used when constructing the nomogram.

Validation of nomogram

The nomogram was validated internally using the training set and externally using the validation set. The discrimination and calibration were performed by bootstrapping with 1,000 resamples to validate the performance of the nomogram in both internal and external datasets.^[14, 15] Discrimination of the nomogram was

assessed using Harrell's C-index, which can estimate the probability between the observed and predicted outcome of distant metastasis.^[13, 16] A calibration plot was obtained based on the binary models to compare the predicted probabilities by the nomogram with the actual probabilities.

RESULTS

Patients and characteristics

A total of 411 elderly patients with complete information were identified after filtering patient data and were included in the study (**Figure 1**), of which 260 patients were assigned into training set and 151 patients were assigned into validation set. Demographic, clinical, and pathological characteristics are listed in **Table 1**.

Independent risk factors and the nomogram

According to the univariate logistic proportional hazard analysis for distant metastasis with the training set, tumor site, histological grade, T stage, and N stage were identified and included in the multivariate logistic proportional hazard analysis. As shown in **Table 2**, tumor site in pancreas (body or tail: odds ratio [OR]=2.282, 95% confidence interval [CI]: 1.174–4.436, $P<0.05$), histological grade (poorly differentiated/undifferentiated: OR=2.600, 95% CI:

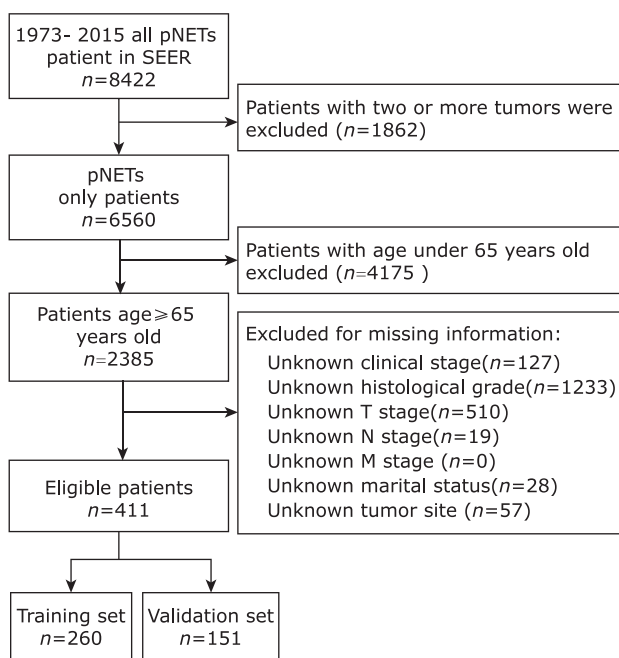


Figure 1. The flow chart of patient selection and screening from the SEER database

Table 1. Demographic, clinical and staging characteristics of training cohort and validation cohort [n(%)]

Characteristics	Training cohort (n=260)	Validation cohort (n=151)
Age at diagnosis of pNETs (yrs)		
65-74	162 (62.3)	108 (71.5)
≥75	98 (37.7)	43 (28.5)
Sex		
Male	147 (56.5)	84 (55.6)
Female	113 (43.5)	67 (44.4)
Race		
White	211 (81.2)	130 (86.1)
African American	17 (6.5)	16 (10.6)
Others*	32 (12.3)	5 (3.3)
Year of diagnosis		
2004-2009	90 (34.6)	24 (15.9)
2010-2014	170 (65.4)	127 (84.1)
Tumor site		
Head of pancreas	98 (37.7)	65 (43.0)
Body or tail of pancreas	141 (54.2)	75 (49.7)
Overlap [#]	21 (8.1)	11 (7.3)
Histological grade		
Well/moderate differentiated	201 (77.3)	117 (77.5)
Poor/undifferentiated	59 (22.7)	34 (22.5)
T stage (6 th edition)		
T1	46 (17.7)	33 (21.9)
T2	100 (38.5)	61 (40.4)
T3	99 (38.1)	43 (28.5)
T4	15 (5.8)	14 (9.3)
N stage (6 th edition)		
N0	174 (66.9)	101 (66.9)
N1	86 (33.1)	50 (33.1)
M stage		
M0	158 (60.8)	91 (60.3)
M1	102 (39.2)	60 (39.7)
Marital status		
Unmarried [‡]	93 (35.8)	44 (29.1)
Married	167 (64.2)	107 (70.9)

* including American Indian/AK Native, Asian/Pacific islander; [#] The junction area of pancreatic head and body; [‡] including never married, divorced, widowed, separated, unmarried or domestic partner

1.266–5.339, $P<0.05$), T stage (T2: OR=8.913, 95% CI=1.985–40.010, $P<0.05$; T3: OR=11.83, 95% CI=2.530–55.350, $P<0.05$; T4: OR=68.650, 95% CI: 8.020–587.600, $P<0.05$), and N stage (N1: OR=3.480, 95% CI: 1.807–6.703, $P<0.05$) were identified as

independent risk factors for distant metastasis of pNETs in elderly patients.

Base on the identified 4 risk factors, a nomogram was developed, as shown in **Figure 2**. Each variable value has its point (0–100 points by default) which is vertically correlated to the integral line at the top of the nomogram. By adding points of the four variables, the total point of an individual pNETs patient can then be obtained, based on which the risk value of distant metastasis can be obtained by vertically referring to the prediction line, *i.e.*, the “risk of metastasis” at the

bottom of the nomogram.

Validation of the nomogram

For the nomogram’s ability to predict distant metastasis in elderly pNETs patients, the internal validation yielded a C-index value of 0.809 (95% *CI*: 0.757–0.861), and the external validation yielded a C-index value of 0.795 (95% *CI*: 0.723–0.867). The calibration curve of the training set and the validation set shows that the predicted distant metastasis rate was in excellent agreement with the observed values (**Figure 3**).

Table 2. Logistic analyses on metastasis of elderly pNETs patients with the training cohort

Variables*	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age at diagnosis (y/d)				
65-74	Reference			
≥75	1.112 (0.666-1.857)	0.684		
Sex				
Male	Reference			
Female	0.916 (0.554-1.515)	0.733		
Race				
White	Reference			
The African American	1.701 (0.631-4.584)	0.294		
Others	0.592 (0.261-1.341)	0.209		
Marital status				
Unmarried	Reference			
Married	0.899 (0.536-1.510)	0.688		
Year of diagnosis				
2004-2009	Reference			
2010-2014	0.826 (0.491-1.391)	0.472		
Site of the tumor				
Head of pancreas	Reference		Reference	
Body / tail of pancreas	1.084 (0.635-1.852)	0.768	2.282 (1.174-4.436)	0.015
Overlap	3.600 (1.328-9.756)	0.012	4.659 (1.471-14.760)	0.009
Histological grade				
Well / moderate differentiated	Reference		Reference	
Poor / undifferentiated	3.202 (1.756-5.836)	0.000	2.600 (1.266-5.339)	0.009
T stage				
T1	Reference		Reference	
T2	11.85 (2.709-51.80)	0.001	8.913 (1.985-40.010)	0.004
T3	24.34 (5.591-106.0)	0.000	11.830 (2.530-55.350)	0.002
T4	143.0 (18.310-1117)	0.000	68.650 (8.020-587.600)	0.000
N stage				
N0	Reference		Reference	
N1	5.194 (2.976-9.065)	0.000	3.480 (1.807-6.703)	0.000

OR, odds ratio; CI, confidence interval.

*Variables in univariate analysis with *P* < 0.1 further underwent multivariate analyses.

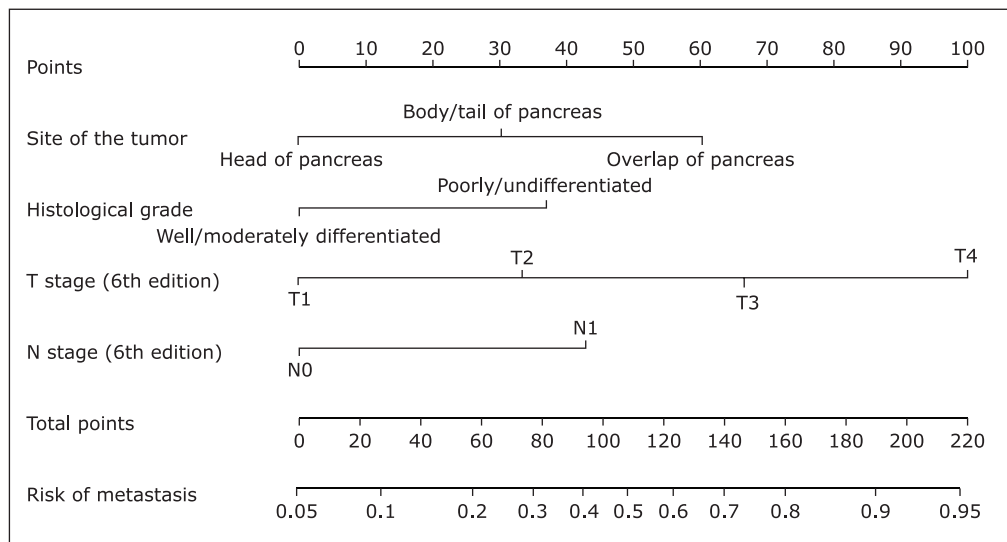


Figure 2. Nomogram for predicting risk of distant metastasis in elderly pNETs patients (≥ 65 years old)

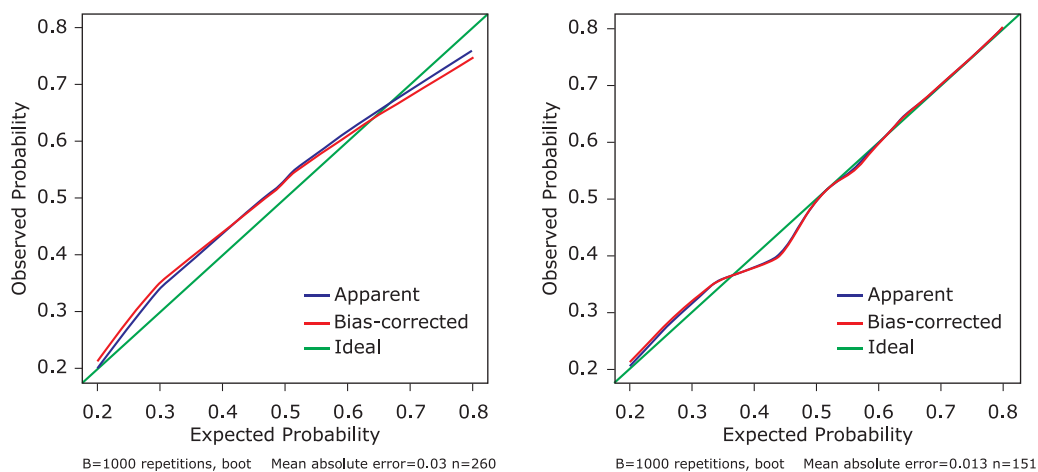


Figure 3. The calibration curves for predicting distant metastasis in elderly pNETs patients by the established nomogram (A) Of the training cohort (internal calibration). (B) Of the validation cohort (external calibration). The “Apparent” and “Bias-corrected” lines represent perfect agreement between the predicted probabilities (x-axis) and the actual probabilities (y-axis). A perfectly accurate nomogram prediction model would result in a plot where the actual and predicted probabilities fall along the 45° line.

DISCUSSION

According to our previous study, pNETs in elderly patients showed different demographic and tumor characteristics from young patients. Of pNETs patients, the proportions of the African Americans and married people in elderly were lower than that of young patients, the proportion of poorly differentiated tumors was higher than that of young patients; less tumor resection and lymph node dissection were done in elderly patients, and the prognosis of elderly patients was worse than that of young patients.^[17] Besides, it

was found that patients aged 65–74 years with well or moderately differentiated pNETs can benefit from primary lesion surgery.^[3] By far, few studies have focused on predicting models for distant metastasis in elderly patients with pNETs.

Our study found that tumor site, histological grade, T stage, and N stage were independent risk factors associated with distant metastasis of pNETs. With the advances in T stage, N stage, and differentiation grade, the risk for distant metastasis increases. Tumors locate at the head of pancreas are more likely to compress the bile duct or pancreatic duct, resulting in

jaundice or pancreatitis, which render it early detectable; while tumors locate in the pancreatic body or tail do not likely cause symptoms in its early stage, *i.e.*, may be prone to silent growth. Therefore, tumors locate in the body or tail of pancreas may be associated with higher risk of distant metastasis.

In this study, four independent risk factors were quantified and a nomogram was developed to assess the risk of distant metastasis for individual patient. We evaluate the effectiveness in terms of discrimination ability and accuracy. It is generally believed that a model has good discriminative ability when its C-index is greater than 0.75. Calibration curve is generally used to evaluate the accuracy of a predicting model, with a straight line fitting carried out on scatter diagram. The farther the straight line with a slope of 45 degrees from the origin, the worse the prediction accuracy. We validated the nomogram internally with the training set and externally with the validation set. The C-indexes were 0.809 (95% *CI*: 0.757–0.861) and 0.795 (95% *CI*: 0.723–0.867), respectively, which indicate the excellent discriminative ability in predicting metastasis. The calibration curves from the training set and validation set present satisfactory lines, indicating the nomogram had excellent accuracy. The established nomogram could be helpful for individual assessment of metastasis and therapeutic decision-making in elderly pNETs patients.^[18-20]

There are two limitations to the current study. First, biomarker ki-67, the index representing tumor proliferation, was not included as a variable in this study because the data is not available in the SEER database. Second, because of the low incidence of pNETs in local elderly population, we had not accumulated enough pNETs patients from our own hospital to externally validate the nomogram, so the application value of the established monogram in Asian population need to be determined in future.

To conclude, through data analyses of elderly pNETs patients in SEER database, we found tumor site of pancreas, histological grade, T stage, and N stage are independent prognostic factors for distant metastasis of pNETs. Further, we established a nomogram based on the four independent prognostic factors to predict distant metastasis in elderly pNETs patients, and performed validations of the model, which showed good discriminative ability and accuracy in predicting distant metastasis in elderly pNETs patients. This study provides a reference for individualized tumor evalua-

tion and treatment options.

Conflict of interests

None.

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