ORIGINAL ARTICLE

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

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Key words: nomogram; pancreatic neuroendocrine tumor; distant metastasis; elderly patients

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.

REFERENCES

1. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the united states. *JAMA Oncol* 2017; 3(10):1335-42. doi: 10.1001/jamaoncol.2017.0589.
2. Hallet J, Law CH, Cukier M, et al. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer* 2015; 121(4):589-97. doi: 10.1002/cncr.29099.
3. Zhang J, Peng CS, Tian YH. Primary site surgery for elderly patients with distant metastatic pancreatic neuroendocrine tumor: to do or not to do? *Clin Interv Aging* 2019; 14:1419-32. doi: 10.2147/cia.S209428.
4. Bertani E, Fazio N, Botteri E, et al. Resection of the primary pancreatic neuroendocrine tumor in patients with unresectable liver metastases: possible indications for a multimodal approach. *Surgery* 2014; 155(4):607-14. doi: 10.1016/j.surg.2013.12.024.
5. Bilimoria KY, Talamonti MS, Tomlinson JS, et al. Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: analysis of 3851 patients. *Ann Surg* 2008; 247(3):490-500. doi: 10.1097/SLA.0b013e31815b9cae.
6. Frilling A, Clift AK. Therapeutic strategies for neuroendocrine liver metastases. *Cancer* 2015; 121(8):1172-86. doi: 10.1002/cncr.28760.
7. Cheng KK, Lim EY, Kanesvaran R. Quality of life of elderly patients with solid tumours undergoing adjuvant cancer therapy: a systematic review. *BMJ open* 2018; 8(1):e018101. doi: 10.1136/bmjopen-2017-018101.
8. Soto-Perez-de-Celis E, Cordoba R, Girones R, et al. Cancer and aging in Ibero-America. *Clin Transl Oncol* 2018; 20 (9):1117-26. doi: 10.1007/s12094-018-1844-1.
9. Shamali A, De'Ath HD, Jaber B, et al. Elderly patients have similar short term outcomes and five-year survival compared to younger patients after pancreaticoduodenectomy. *Int J Surg* 2017; 45: 138-43. doi: 10.1016/j.ijssu.2017.07.106.
10. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence - SEER

- Research Data, 9 Registries, Nov 2020 Sub (1973-2015).
11. Surveillance Research Program, National Cancer Institute SEER*Stat software, version <8.3.9.2>. Available from <https://seer.cancer.gov/seerstat/>.
  12. R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available from <https://www.R-project.org/>.
  13. Li G, Tian ML, Bing YT, et al. Impact of a prior non-pancreatic malignancy on survival outcomes of patients with stage IV pancreatic neuroendocrine tumor: A population-based and propensity score matching study. *Pancreas* 2020; 49(8):1090-8. doi: 10.1097/MPA.0000000000001630.
  14. Salarbaks AM, Lindeboom R, Nijmeijer W. Pneumonia in hospitalized elderly hip fracture patients: the effects on length of hospital-stay, in-hospital and thirty-day mortality and a search for potential predictors. *Injury* 2020; 51(8):1846-50. doi: 10.1016/j.injury.2020.05.017.
  15. Guo R, Wang B, Wang Y, et al. Epidemiological analysis and the nomogram for possible risk factors for severe microtia. *J Craniofac Surg* 2021; 32(2): e184-e189. doi: 10.1097/scs.0000000000007068.
  16. D'Arrigo G, Gori M, Pitino A, et al. Statistical methods to assess the prognostic value of risk prediction rules in clinical research. *Aging Clin Exp Res* 2021; 33(2):279-83. doi: 10.1007/s40520-020-01542-y.
  17. Li G, Tian ML, Bing YT, et al. Clinicopathological features and prognosis factors for survival in elderly patients with pancreatic neuroendocrine tumor: A STROBE-compliant article. *Medicine* 2019; 98(11): e14576. doi: 10.1097/md.00000000000014576.
  18. Balachandran VP, Gonen M, Smith JJ, et al. Nomograms in oncology: more than meets the eye. *Lancet Oncol* 2015; 16 (4):e173-80. doi: 10.1016/s1470-2045(14)71116-7.
  19. Liang W, Zhang L, Jiang G, et al. Development and validation of a nomogram for predicting survival in patients with resected non-small-cell lung cancer. *J Clin Oncol* 2015; 33(8):861-9. doi: 10.1200/jco.2014.56.6661.
  20. Pierorazio PM, Patel HD, Johnson MH, et al. Distinguishing malignant and benign renal masses with composite models and nomograms: A systematic review and meta-analysis of clinically localized renal masses suspicious for malignancy. *Cancer* 2016; 122(21):3267-76. doi: 10.1002/cncr.30268.

论著

使用列线图预测老年胰腺神经内分泌肿瘤患者 手术前远处转移的风险

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摘要

目的 建立一个列线图来预测老年患者胰腺神经内分泌肿瘤 (pancreatic neuroendocrine tumors, pNETs) 远处转移的风险。

方法 从美国“肿瘤监测、流行病学和预后 (Surveillance, Epidemiology, and End Results, SEER) 数据库”中提取 1973 年至 2015 年之间年龄 ≥ 65 岁 pNETs 患者的数据。所有符合条件的患者随机分为训练队列和验证队列。对训练队列进行单因素和多因素 Logistic 回归分析以确定远处转移的独立风险因素。使用 R 软件的 rms 软件包基于独立风险因素开发列线图。使用 C 指数和校准曲线在训练队列进行内部验证, 在验证队列进行外部验证。

结果 研究共确定了 411 名老年 pNETs 患者, 260 名被分配到训练队列, 151 名被分配到验证队列。单因素和多因素 Logistic 回归分析表明, 肿瘤部位 (胰腺体 / 尾: 比值比 [OR]=2.282; 95% 可信区间 [CI]: 1.174–4.436, $P<0.05$), 组织学分级 (低分化 / 未分化: OR=2.600, 95% CI: 1.266–5.339, $P<0.05$), T 分期 (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, $P<0.05$) 和 N 分期 (N1: OR=3.480, 95% CI: 1.807–6.703, $P<0.05$) 被确定为老年人 pNETs 远处转移的独立危险因素。列线图显示出良好的预测准确性, 内部验证的 C 指数为 0.809 (95% CI: 0.757–0.861), 外部验证的 C 指数为 0.795 (95% CI: 0.723–0.867), 预测的远处转移率与校准曲线的观察值吻合良好。

结论 我们建立的列线图在评估老年 pNETs 患者远处转移风险方面具有较好的辨别能力和准确性, 可为老年 pNETs 患者的个体化评估和治疗决策提供参考。

关键词: 列线图; 胰腺神经内分泌肿瘤; 远处转移; 老年患者

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