ORIGINAL ARTICLE

Does Prior Cancer Have an Influence on the Survival Outcomes of Patients with Localized Pancreatic Neuroendocrine Tumors?

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Objective To investigate the impact of prior non-pancreatic cancer on the survival outcomes of patients with localized pancreatic neuroendocrine tumors (PanNETs).

Methods We reviewed the Surveillance, Epidemiology, and End Results database and selected patients with localized PanNETs diagnosed between 1973 and 2015. We divided the patients into two groups according to the presence or absence of prior non-pancreatic malignancy. Before and after propensity score matching, we compared the clinicopathological characteristics and studied the overall survival and cancer-specific survival.

Results A total of 357 (12.9%) of 2778 patients with localized PanNETs had prior cancer. A total of 1211 cases with only a localized PanNET and 133 cases with a localized PanNET and prior cancer had complete data and met the inclusion criteria of the current study. Patients with prior cancer were associated with advanced age (>65 years, 57.9% prior cancer vs. 31.0% no prior cancer, $P<0.001$), later year of diagnosis (87.2% vs. 80.2%, $P=0.049$), a higher proportion of poorly differentiated/undifferentiated grade tumors (4.5% vs. 1.5%, $P=0.025$), and a higher proportion of no primary site surgery (19.5% vs. 10.4%, $P=0.003$). Prostate (29.32%), breast (18.05%), other genitourinary and retroperitoneal (16.54%), and gastrointestinal (12.78%) cancers were the most common prior cancer types. Most of the prior cancers (95.49%) were localized and regional, and only 4.51% of the prior cancers were distant. Patients with interval periods between the prior cancer and PanNET of ≤ 36 months, 36–60 months, 60–120 months, and >120 months accounted for 33.08%, 13.53%, 24.06%, and 29.32% of all cases with prior cancers, respectively. Univariate and multivariate Cox proportional hazards

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analyses were performed. The presence/absence of prior cancers did not impact survival outcomes of patients with localized PanNETs before and after propensity score matching (PSM). Further subgroups analysis showed that, patients with localized PanNETs and prior distant cancer had worse cancer-specific survival than patients with prior local/regional cancer or patients without prior cancer ($P<0.001$). No significant differences in cancer-specific survival were observed in terms of the different sites of the prior cancers and the different interval periods of prior cancers and PanNETs ($P<0.05$).

Conclusions Patients with localized PanNETs and a history of prior cancer had survival outcomes that were comparable to those of patients with no history of prior cancer. Patients with localized PanNETs and prior cancer could be candidates for clinical trials if they satisfy all other conditions; aggressive and potentially curative therapies should be offered to these patients.

NEUROENDOCRINE tumors (NETs) originate from the neuroendocrine cells and represent a heterogeneous group of neoplasms with various biological characteristics and behavior. Pancreatic NET (PanNET) is a rare pancreatic neoplasm with an annual incidence of 0.19/100 000–0.32/100 000,^[1–3] which has been rising in the United States over the past decades.^[4] PanNETs account for approximately 5% of all neuroendocrine tumors and 1%–2% of all pancreatic malignancies.^[5, 6] PanNET is a malignant neoplasm that differs greatly in biological behavior. Most PanNETs are characterized by a low malignant behavior and slow growth rate, and some of them have a strong invasive ability, which may lead to invasive and lethal metastasis.^[1] With the popularization of health examination and the improvement of examination tools, more localized PanNETs have been found. Surgery is the only curative treatment option for patients with localized PanNETs. Patients with localized PanNETs have a better prognosis and longer survival time. The 5-year survival rate for localized PanNETs is 79%, and the median survival period is 136 months.^[3]

Patients with prior cancer have a higher risk of developing secondary cancer in the subsequent survival time.^[7] Possible causes include a genetic tendency and common environmental risk factors.^[8, 9] Patients with malignancy and prior cancer were more likely to be excluded from clinical trials and radical surgery due to the possible impact of the prior cancer.^[10, 11] However, many studies have revealed that prior cancer did not have a disadvantageous impact on the survival of patients.^[12, 13] Therefore, it has become the focus of whether prior cancer has an impact on the survival of patients with localized PanNET. Considering that the impact of prior cancer is more likely demonstrated during the longer survival time of patients with local-

ized PanNETs, the impact of prior cancer on patients with localized PanNETs may be different from that of other cancer patients. The aim of the current study was to investigate the impact of prior cancer on the survival of patients with a subsequent localized PanNET.

MATERIALS AND METHODS

Data source and cohort selection

We searched the data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database, using SEER*stat software (version 8.3.5). Among these databases, the SEER 18 Registries was used, which covers approximately 27.8% of the United States population (based on the 2010 census) from year of 1973 to 2015, and covers the following geographic areas: San Francisco-Oakland, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska, rural Georgia, California (excluding SF/SJM/LA), Kentucky, Louisiana, New Jersey, and Greater Georgia.

We selected patients with localized PanNETs diagnosed between 1973 and 2015. We only included patients with diagnoses based on histological studies and excluded those whose diagnoses relied only on autopsies or were detailed only on death certificates. PanNET was defined as including the following International Classification of Diseases for Oncology third edition (ICD-O3) codes: 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, 8249/3. All pancreatic anatomical sites were included (C25.0–C25.9) in the study.

We identified a total of 9457 patients with PanNETs diagnosed between 1973 and 2015 in the SEER database, of which 2778 had localized PanNETs. We

selected 1942 patients with only one primary cancer of localized PanNET, and 357 patients with localized PanNET and one prior cancer. We further selected patients with complete data, and those with a survival time of more than 1 month in the two groups, and selected patients with an interval period of more than 6 months in the second group.

Specifically, the exclusion criteria included: patients with a survival time of less than 1 month, patients with unknown survival, a history of another primary pancreatic malignancy, a history of more than one primary malignancy before PanNET, a history of one or more malignancies after the diagnosis of PanNET, and/or a history of a prior malignancy diagnosed within 6 months prior to stage IV PanNET (to exclude the possibility of simultaneous malignancies).

Data collection

We collected the following variables: age at diagnosis, sex, race, marital status, year of diagnosis (PanNET), site of the PanNET in the pancreas, histological grade of the PanNET, tumor size, primary site surgery, survival status, cause of death, and survival months. In addition, in the cases with prior cancer, we also collected data on the primary site, clinical stage of prior cancer, and the interval period between the two malignancies. According to the different interval periods between the two cancers (≤ 36 months, 36–60 months, 60–120 months, and >120 months), patients with prior cancer were divided into four groups.

Outcome measurement

The primary outcomes were overall survival (OS) and cancer-specific survival (CSS). Patients were followed until the date of death or censored at the end of 2015. We compared the survival outcomes between the patients with and without prior cancer before and after variable Propensity Score Matching (PSM) to investigate the impact of prior cancer.^[14] PSM is a statistical method to solve the problem of selection bias (that is, to control confounding factors). PSM is to use propensity score value to find one or more individuals with the same or similar background characteristics from the control group for each individual in the treatment group. In this way, the interference of other confounding factors is minimized.^[15] Moreover, the PanNET CSS according to the prior cancer sites and the interval periods between any prior cancer and PanNET were also measured.

Statistical analysis

We performed the analysis using IBM SPSS Statistics 22.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 7.0 (GraphPad Software, USA). We presented the characteristics of the prior cancers using descriptive statistics. The type, stage of prior cancer, and interval period were quantified. We performed a PSM by the "MatchIt" R package with the "nearest neighbor matching" method (ratio = 2:1) regarding age, year of diagnosis, histological grade, and primary site surgery to balance the potential baseline confounding variables between the two groups.^[16] We performed *Chi-square* tests before and after PSM to compare the characteristics of patients with and without a prior history of cancer. We performed Kaplan-Meier survival analysis, plotted survival curves, calculated the CSS and OS rates, and compared survival time in different groups using a *log-rank* test. Additionally, we performed a univariate and multivariate Cox proportional hazards model to identify the variables associated with CSS and OS. A two-sided *P*-value <0.05 was considered statistically significant. Hazard ratios (HRs) are presented with 95% confidence intervals (95%CI).

RESULTS

Adjusting for patient characteristics with propensity score matching

The patient screening process is shown in **Fig. 1**. A total of 1211 patients with only one localized PanNET and 133 cases with localized PanNET and a history of prior cancer had complete data and met the inclusion criteria of the current study. A total of 357 (12.9%) of 2778 patients with localized PanNETs had prior cancer. Their clinicopathological characteristics are listed in **Table 1**. Patients with prior cancer were associated with advanced age (>65 years, 57.9% prior cancer vs. 31.0% no prior cancer, $P<0.001$), later year of diagnosis (87.2% vs. 80.2%, $P=0.049$), a higher proportion of poorly differentiated/undifferentiated grade tumors (4.5% vs. 1.5%, $P=0.025$), and a higher proportion of no primary site surgery (19.5% vs. 10.4%, $P=0.003$). After PSM, none of the characteristics differed between the two groups.

The primary site and clinical stage of the prior cancer are depicted in **Fig. 2A**. Prostate (29.32%), breast (18.05%), other genitourinary and retroperitoneal (16.54%), and gastrointestinal (12.78%) cancers were the most common prior cancer types. Most of the

Figure 1. Cases management process.

PanNET: pancreatic neuroendocrine tumor.

prior cancers (95.49%) were localized and regional, and only 4.51% of prior cancers were distant (**Fig. 2B**). The median interval between the prior cancer and the subsequent localized PanNET was 66 months (range, 7–374 months). **Fig 2C** illustrates the interval periods according to the different sites of the prior cancer. Patients with interval periods between two malignant cancers of ≤ 36 months, 36–60 months, 60–120 months, and >120 months accounted for 33.08%, 13.53%, 24.06%, and 29.32% of all cases with prior cancers, respectively (**Fig 2D**).

Kaplan-Meier analysis with log-rank test, univariable and multivariable Cox proportional hazards analysis before and after PSM

The Kaplan-Meier analysis and log-rank test demonstrated similar OS and CSS between the patients with and without prior cancer, either before or after PSM (**Fig. 3**). Univariate and multivariate Cox proportional hazards analyses were performed for OS and CSS in the overall cohort ($n=1344$) before PSM (**Table 2** and **Table 3**). The presence/absence of prior cancers did not affect OS and CSS in patients with localized PanNET before PSM. Patients with older age (>65 years), larger tumor size (>4 cm), and poorly differentiated/undifferentiated tumor grade had lower OS and CSS. Patients with the diagnosis year of 2011–2015 had a comparable OS and disadvantage CSS. Patients who underwent primary site surgery had both better OS and CSS.

After PSM, univariate and multivariate Cox proportional hazards analyses were also performed

($n=399$). Patients with poorly/undifferentiated tumors had poor OS ($HR=5.028$, 95%CI 2.068–12.228, $P<0.001$) and CSS ($HR=42.33$, 95%CI 6.694–267.7, $P<0.001$). Primary site surgery of PanNET was shown to improve patients' OS ($HR=0.216$, 95%CI 0.111–0.420, $P<0.001$) and CSS ($HR=0.105$, 95%CI 0.015–0.720, $P=0.022$).

Further Kaplan-Meier analysis with the log-rank test in the subgroups of patients with prior cancers after PSM

Further Kaplan-Meier analysis with the log-rank test revealed the CSS curves stratified by the clinical stage, site of the prior cancers, and interval period (**Fig. 4**). Patients with localized PanNET and prior distant cancer had worse CSS than patients with prior local/regional cancer or those with no prior cancer ($P<0.001$). No significant differences were observed in terms of the different sites of the prior cancer and interval period groups ($P>0.05$).

DISCUSSION

As is well known, patients with cancer have a higher risk of developing a secondary malignancy in the subsequent survival period.^[7, 17–19] Reportedly, 18% of patients with cancer in the United States have a history of cancer according to the data from the SEER database.^[20] In the present study, 12.9% (357/2778) of the patients with localized PanNET proved to have had prior cancer. Malignancies in the

Table 1. Characteristics of patients with localized PanNET included in the study [*n* (%)]

Variables	Before PSM				After PSM			
	NPC	PC	χ^2	<i>P</i>	NPC	PC	χ^2	<i>P</i>
<i>n</i>	1211	133			266	133		
Age (yrs)			38.93	<0.001			0.187	0.667
≤65	836 (69.0)	56 (42.1)			106 (39.8)	56 (42.1)		
>65	375 (31.0)	77 (57.9)			160 (60.2)	77 (57.9)		
Gender			0.347	0.584			0.005	1.000
Male	623 (51.4)	72 (54.1)			145 (54.5)	72 (54.1)		
Female	588 (48.6)	61 (45.9)			121 (45.5)	61 (45.9)		
Race			0.183	0.913			0.367	0.832
White	943 (77.9)	102 (76.7)			211 (79.3)	102 (76.7)		
Black	131 (10.8)	16 (12.0)			28 (10.5)	16 (12.0)		
Other	137 (11.3)	15 (11.3)			27 (10.2)	15 (11.3)		
Marital status			0.624	0.437			0.024	0.907
Married	815 (67.3)	94 (70.7)			190 (71.4)	94 (70.7)		
Unmarried	396 (32.7)	39 (29.3)			76 (28.6)	39 (29.3)		
Year of diagnosis				0.049				0.368
1973-2010	240 (19.8)	17 (12.8)			40 (15.0)	17 (12.8)		
2011-2015	971 (80.2)	116 (87.2)			226 (85.0)	116 (87.2)		
Tumor site (pancreas)			3.836	0.428			1.234	0.745
Head	294 (24.3)	34 (25.6)			61 (22.9)	34 (25.6)		
Body/tail	707 (58.4)	75 (56.4)			165 (62.0)	75 (56.4)		
Overlap	68 (5.6)	4 (3.0)			7 (2.6)	4 (3.0)		
Other	142 (11.7)	20 (15.0)			33 (12.4)	20 (15.0)		
Histological grade			6.252	0.025			0.130	0.788
Well/moderately	1193 (98.5)	127 (95.5)			256 (96.2)	127 (95.5)		
Poorly/undifferentiated	18 (1.5)	6 (4.5)			10 (3.8)	6 (4.5)		
Tumor size (cm)			4.283	0.117			0.242	0.886
≤2	657 (54.3)	82 (61.7)			159 (59.8)	82 (61.7)		
2-4	360 (29.7)	38 (28.6)			77 (28.9)	38 (28.6)		
>4	194 (16.0)	13 (9.8)			30 (11.3)	13 (9.8)		
Primary site surgery			9.990	0.003			0.000	1.000
No	126 (10.4)	26 (19.5)			52 (19.5)	26 (19.5)		
Yes	1085 (89.6)	107 (80.5)			214 (80.5)	107 (80.5)		

PSM: propensity score matching; NPC: no prior cancer; PC: prior cancer.

Race: Other included American Indian/AK Native Asian/ Pacific Islander. Marital status: Unmarried included Divorced/ Separated/Single (never married)/Unmarried or Domestic partner/Widowed. Tumor site: "Other" included Islets of langerhans+other specific parts of pancreas+pancreas, NOS of pancreas.

prostate (29.32%), breast (18.05%), genitourinary system and retroperitoneum (16.54%), and gastrointestinal tract (12.78%) were the most common types of the prior cancers, most of which were local or regional (95.49%). The patients whose prior cancers were gynecologic cancers revealed the longest interval time between the prior cancer and PanNET (me-

dian 97.5 months, range 8-254 months), and those with gastrointestinal cancers showed the shortest interval (median 16 months, range 7-181 months). Approximately one-third of the patients (33.08%) had an interval period of less than 36 months. More than half of the patients (53.38%) had an interval period of more than five years. These findings may provide

Figure 2. Proportion of site of prior cancer (A); Proportion of the stage of prior cancer (B); Box-graph of interval period according to site of prior cancer (C); Proportion of patients with different interval month period between the prior cancer and the subsequent localized PanNET (D).

Figure 3. Overall survival and cancer-specific survival in localized PanNET patients with and without prior cancers before and after PSM. (A) Kaplan-meier analysis for overall survival in patients with and without prior cancers before PSM; (B) Kaplan-meier analysis for cancer-specific survival in patients with and without prior cancers before PSM; (C) Kaplan-meier analysis for overall survival in patients with and without prior cancers after PSM; (D) Kaplan-meier analysis for cancer-specific survival in patients with and without prior cancers after PSM.

some information that could be helpful in the follow-up of these patients.

Cancer patients with a history of cancer were more likely to be excluded from clinical trials because

of concerns about the impact of the prior cancers on the trial outcomes.^[10, 11] However, excluding such a large portion of cohorts may negatively influence the enrollment and universality of clinical trials. Previous

Table 2. Results of univariate and multi-variate Cox proportional hazard regression analyses for overall survival

Variables	Before PSM					After PSM				
	Univariate analysis (P value)	Estimates of coefficient of correlation	Standard error	Wald χ^2	HR	95%CI	P	Univariate analysis (P value)	Estimates of coefficient of correlation	Standard error
Prior cancer	0.060						0.347	0.964		
No										
Yes										
Age (yrs)	0.000				1 (Referent)		0.000	0.053		0.178
≤65										
>65		1.219	0.234	27.19	3.383	2.140-5.348	0.000			
Gender	0.115						0.210	0.510		
Male										
Female										
Race	0.844							0.305		
White										
Black										
Other										
Marital status	0.364							0.659		
Married										
Unmarried										
Year of diagnosis	0.400							0.527		
1973-2010										
2011-2015										
Tumor site	0.904							0.491		
Head										
Body or tail										
Other										
Histological grade	0.002				1 (Referent)		0.002	0.001		0.000
Well/moderately										
Poorly/undifferentiated		1.222	0.399	9.378	3.396	1.553-7.425			1.615	12.69
Tumor size (cm)	0.021						0.016	0.956		5.028
≤2										2.068-12.228
2-4		-0.008	0.272	0.001	0.992	0.582-1.691	0.978			0.000
>4		0.695	0.264	6.929	2.004	1.194-3.362	0.008			
Primary site surgery	0.000						0.000	0.000		
No					1 (Referent)					
Yes		-1.554	0.237	43.042	0.211	0.133-0.336	0.000		-1.532	20.474
										0.111-0.420

Variables with univariate analysis $P < 0.15$ underwent further multivariate analysis.

Table 3. Results of univariate and multi-variate Cox proportional hazard regression analyses for cancer specific survival

Variables	Before PSM						After PSM					
	Univariate analysis (P value)	Estimates of coefficient of correlation	Standard error	Wald χ^2	HR	P	Univariate analysis (P value)	Estimates of coefficient of correlation	Standard error	Wald χ^2	HR	P
Prior cancer	0.418						0.500					
No												
Yes												
Age (yrs)	0.002						0.812					
≤65					1(Referent)							
>65					2.958	1.228-7.127	0.016					
Gender	0.525						0.167					
Male												
Female												
Race	0.979						0.260					
White												
Black												
Other												
Marital status	0.621						0.662					
Married												
Unmarried												
Year of diagnosis	0.011						0.890					
1973-2010					1(Referent)							
2011-2015		1.290	0.533	5.864	3.633	1.279-10.320	0.015					
Tumor site	0.615						0.480					
Head												
Body or tail												
Other												
Histological grade	0.001					0.000	0.000					
Well/moderately					1(Referent)							
Poorly/undifferentiated		2.191	0.573	14.635	8.945	2.911-27.486	0.000				1(Referent)	
Tumor size (cm)	0.012						0.682					
≤2					1(Referent)							
2-4		0.183	0.591	0.096	1.201	0.377-3.828	0.757					
>4		1.159	0.544	4.545	3.186	1.098-9.245	0.033					
Primary site surgery	0.000					0.000	0.017					
No					1(Referent)						1(Referent)	
Yes		-1.835	0.468	15.40	0.160	0.064-0.399	0.000				0.105	0.015-0.720
									0.984	5.259		0.022

Figure 4. Kaplan-Meier analysis for cancer-specific survival stratified by the clinical stage, site of the prior cancers, and interval period groups. (A) Kaplan-Meier analysis for cancer-specific survival stratified by the clinical stage of prior cancer; (B) Kaplan-Meier analysis for cancer-specific survival stratified by the site of prior cancer; (C) Kaplan-Meier analysis for cancer-specific survival stratified by the interval month groups.

studies have focused on the impact of prior cancers on cancer patients, which included patients with glioblastoma multiforme,^[13] locally advanced lung cancer,^[12] and stage IV pancreatic ductal adenocarcinoma.^[21] These tumors are relatively aggressive, and neither of the above studies has seen any disadvantage of prior cancers on the survival of cancer patients. However, to the best of our knowledge, little information has been available focusing on whether the history of a prior non-pancreatic cancer has an impact on the survival of patients with localized PanNET. For patients with localized PanNET, which are relatively inert tumors with longer survival times, we hypothesize that prior cancers may have an impact on their survival. The current study revealed that prior local or regional cancers did not affect the survival of patients with localized PanNET, whereas patients with prior distant cancers had a shorter CSS. (**Fig. 4A**)

Radical resection is supposed to be the most effective treatment for localized PanNET, but the pres-

ent study shows that the proportion of patients with prior cancer undergoing surgery is significantly lower than that of patients without prior cancer (80.5% vs. 89.6%, $P=0.003$). It is commonly believed that patients with prior malignancies have a poor prognosis, poor tolerance of surgery, and that the treatment of the prior cancers may affect the treatment of the new cancer. Our study found that prior distant cancers had a small effect on the survival outcome of patients with localized PanNET, whereas prior local or regional cancers had no effect on the survival outcome of patients with localized PanNET. This also suggests that patients with localized PanNET and prior local or regional cancers should be preferred to undergo surgery if otherwise appropriate.

Most PanNETs are sporadic; however, they may also occur in patients susceptible to certain syndromes, such as multiple endocrine neoplasm type 1 (MEN1), von Hippel-Lindau syndrome (VHL), neurofibromatosis type 1 (NF1), and joint sclerosis syndrome

(TSC).^[22, 23] Genome mutations always occur in patients with PanNET and familial syndromes. However, the SEER database does not have information about gene mutations in patients. To exclude patients with familial syndromes, the design of this study focused on the following points: (a) There was only one malignant PanNET in the first group; (b) There was only one cancer in the second group before PanNET, and no subsequent cancer; (c) The interval period between the two cancers was more than 6 months. By strictly following the above provisions, we were able to exclude patients with familial syndromes.

There are several limitations that need to be addressed. First, the SEER database did not provide several variables, such as performance status, comorbidities, and Ki-67. Second, therapeutic information was not available for patients who did not undergo surgery. In addition, patients with more than one prior cancer were not analyzed in the present study because the number was limited.

In conclusion, the study found that patients with localized PanNETs and a history of local/regional prior cancer had survival outcomes that were comparable to those of patients without prior cancer. In other words, previous local/regional cancer did not affect the survival of patients with localized PanNET. We inferred that if other conditions are appropriate, aggressive and potentially curative therapies should be offered for these patients. Moreover, patients with localized PanNET and prior local/regional cancer could be candidates for clinical trials if they meet all other conditions;

Availability of Data and Materials All supporting materials were uploaded in <https://pan.baidu.com/s/14W0zDUWOnKbj1Q9hLYgMgw&shfl=sharepset>

Conflicts of Interest Statement All authors have no competing interests to declare.

Compliance with Ethical Standards This study does not include any studies with human participants or animals performed by any of the authors. In addition, according to the guidelines of the government of the United States, data released through the SEER database does not require informed patient consent.

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中文摘要

既往癌症对局限性胰腺神经内分泌肿瘤患者的生存结果有影响吗？

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摘要

目的 探讨既往非胰腺来源的恶性肿瘤对局限性胰腺神经内分泌肿瘤（PanNET）患者生存结局的影响。

方法 我们选取美国肿瘤监测、流行病学和生存结果数据库（the Surveillance, Epidemiology, and End Results database, SEER database）中，1973 年至 2015 年期间诊断为局部 PanNET 的患者进行研究。根据患者既往是否存在非胰腺恶性肿瘤，我们将患者分为两组。在倾向评分匹配前和匹配后，我们比较了两组患者的临床病理特征，并研究了总体生存率和癌症特异性生存率的独立影响因素。

结果 在 2778 例局限性 PanNET 患者中，357 例（12.9%）既往曾患有癌症。在 2778 例患者中，数据资料完整的患者有 1344 例，其中既往无肿瘤病史的患者 1211 例，合并肿瘤病史的患者 133 例。分析发现，既往患有癌症与高龄（65 岁以上，57.9% 既往患有癌症，31.0% 既往无癌症， $P<0.001$ ）、诊断年份较晚（87.2% 比 80.2%， $P=0.049$ ）、低分化 / 未分化级别肿瘤比例较高（4.5% 比 1.5%， $P=0.025$ ）和既往肿瘤未手术比例较高（19.5% 比 10.4%， $P=0.003$ ）相关。前列腺癌（29.32%）、乳腺癌（18.05%）、其他泌尿生殖道癌和腹膜后癌（16.54%）以及胃肠道癌（12.78%）是最常见的既往癌症类型。大多数既往癌症（95.49%）为局限性或区域性肿瘤，只有 4.51% 的患者既往癌症伴远处转移。两个肿瘤发病间隔时间 ≤ 36 个月、36-60 个月、60-120 个月和 >120 个月分别占 33.08%、13.53%、24.06% 和 29.32%。在对两组患者变量进行倾向评分匹配前和匹配后，我们对患者进行了单变量和多变量 Cox 比例风险分析，结果显示匹配前和匹配后，既往癌症的存在与否并不影响局部 PanNET 患者的生存结果。进一步亚组分析显示，既往合并转移癌症的患者 PanNET 特异性生存率比既往局部或区域癌症的患者或既往无癌症的患者生存率低。既往癌症的部位和两种肿瘤的间隔期不影响患者的生存率。

结论 具有既往癌症史的局限性 PanNET 患者的生存结果与无既往癌症史的患者相当。如果其他条件相同，则具有既往癌症史的局限性 PanNET 患者可以作为临床试验的候选患者。此研究结果支持为此类患者的 PanNET 提供更为积极的治疗方法。

关键词：胰腺神经内分泌肿瘤；既往癌症；倾向评分匹配