Clinical Characteristics and Survival Associations of Pancreatic Neuroendocrine Tumor: Does Age Matter?

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Research

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Abstract

Background Pancreatic neuroendocrine tumor (pNET) is the second most common epithelial neoplasm of pancreas. As in pancreatic adenocarcinoma, patients with different onset ages display different clinical features and prognosis, we divided pNET patients into early-onset pancreatic neuroendocrine tumor (EOpNET) and typical age-at-onset pancreatic neuroendocrine tumor (TOpNET) to investigate the effect of onset age on its clinical characteristics and prognosis.

Methods Data were collected from the Surveillance, Epidemiology, and End Results (SEER) database (2004–2015; cohort 1) and Fudan University Shanghai Cancer Center (FUSCC) (2005–2018; cohort 2) retrospectively. The clinical characteristics were compared using chi-squared tests. Cox proportional hazards regression was used to evaluate hazard ratios (HRs) and 95% confidence intervals (CIs), and overall survival were formulated by Kaplan–Meier curves.

Results In total 5,368 and 330 patients' data were included from the SEER database and FUSCC. Gender had no effect on survival in EOpNET group. Tumors locating in the tail (HR: 0.721, 95%CI: 0.63–0.83, $P < 0.001$) and body (HR: 0.712, 95%CI: 0.60–0.85, $P = 0.001$) had lower risks of death compared to tumors in the head in TOpNET group. The overall survival of EOpNET (136 (3-143) months) was better than TOpNET (85 (3-143) months) ($P < 0.001$) in SEER database. The results in FUSCC was similar with SEER cohort.

Conclusions EOpNET group had significantly better overall survival than TOpNET though their clinical characteristics were not significantly different. In the future personalized treatment of pNET, the onset age of patients will become another important factor for guiding the treatment and prognosis.

Background

Pancreatic neuroendocrine tumor (pNET) is the second most common epithelial neoplasm of the pancreas with relatively inert biological behavior compared to pancreatic adenocarcinoma.[1] However the incidence of it has increased steadily in recent decades[2], probably due to more sensitive detection methods and more frequent routine examinations among people.[3, 4] Recent reports suggest that early-onset pancreatic cancer (EOPC) which was defined as pancreatic adenocarcinoma (PDAC) with onset age before 50 and accounts for 5–10% of all pancreatic cancer cases, displays a distinct clinical and/or biological subset of the disease [5–7]. With a mean age at diagnosis of 56.8 for pNET, also a small proportion of cases are diagnosed in younger age[8]. However, research on the differences between early-onset pancreatic neuroendocrine tumor (EOpNET) and typical age-at-onset pancreatic neuroendocrine tumor (TOpNET) are very limited, probably due to difficulties in studying rare disease subset with lower incidence. Most studies are descriptive and only include relatively small populations lacking a typical age at diagnosis comparison group. In the recent report of Wang et al., age plays a critical influence on the overall survival and should be considered as a factor in future staging systems of pNETs[9]. To identify whether onset age of pNET has similar effects in patients as in PDAC, we conducted this study to evaluate the associations between clinical characteristics and prognosis by age at diagnosis of pNET, and how early-onset pNET (EOpNET) differs from typical age-onset pNET (TOpNET).

Methods

Patients and Data Collection

Pathologically confirmed pNET cases from 2004 to 2015 were retrieved from the SEER database. Patients were collected on the basis of International Classification of Diseases for Oncology, 2nd and 3rd editions (ICD-O-2/3) for pancreatic tumors: C25.0 to C25.9. The ICD-O-3 diagnosis codes used for retrieving are as follows: Pancreatic endocrine tumor (8150), Insulinoma (8151), Glucagonoma (8152), Gastrinoma (8153), Vipoma (8155), Somatostatinoma (8156), Carcinoid tumor (8240), Enterochromaffin cell carcinoid (8241), Enterochromaffin-like cell tumor (8242), Goblet cell carcinoid (8243), Neuroendocrine carcinoma (8246), Atypical carcinoid tumor (8249). We collected TNM data according to the following codes: derived the American Joint Committee on Cancer (AJCC) stage group 6th ed (2004+), collaborative stage (cs) tumor size 2004, cs extension 2004, cs lymph nodes 2004, cs metastasis at dx 2004, Regional nodes positive (1988+), and Regional nodes examined (1988+). Baseline clinicopathologic features were retrieved including age, gender, race, surgery, location of the primary site, and differentiation.

And then a single center series of Fudan University Shanghai Cancer Center (FUSCC) was analyzed and patients who were pathologically diagnosed of pNET were included. The data of demographics, including age, sex, grade, location of the primary site and surgery condition were retrieved. And the data of tumor T stage, nodal status and metastases were also retrieved and classified on the basis of the AJCC staging classification (8th). The follow-up data were confirmed by review of medical records monthly and contacting the patients or their relatives to ascertain disease progression and vital status or date of death if applicable.

The study was approved by the ethics committee of Fudan University Shanghai Cancer Center. In both cohorts, patients with overall survival time less than 3 months were excluded to rule out perioperative mortality.

Statistical Analysis

For statistical analysis we defined patients with age < 50 years as early-onset pNET (EOpNET) and age $\geq$ 50 years as typical age-at-onset pNET (TOpNET) at the time of diagnosis. Clinical characteristics were compared using chi-squared tests. Survival time was calculated from the date of initial diagnosis until the date of last follow-up time or time of death. Kaplan-Meier method and log-rank tests were used to analyze the overall survival and compare survival proportions. Univariate survival analysis of age, sex, grade, surgery, tumor location and so on were performed by Cox proportional hazards regression. Hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs) were calculated. All the statistical analyses were performed using IBM SPSS Statistics version 21.0 software (IBM Corp, Armonk, NY, USA) and GraphPad Prism 7.0. All tests were two-sided and tests with P values < 0.05 were considered statistically significant.

Results

In total, 5,368 patients from the SEER database were pathologically diagnosed of pNET and included in the study (Table 1), including 1203 (22.4%) EOpNET patients and 4165 (77.6%) TOpNET patients, respectively. While the male/female ratio was around 1:1 in EOpNET patients (1:1.05) which was similar to previous reports[7, 8], the proportion of male in TOpNET patients was significantly higher than female (1.30:1, $P < 0.001$). Approximately half of the patients had a tumor located in the body and/or tail of the pancreas in both groups (45.2% and 48.1%). 92.5% and 89.4% patients had low or intermediate differentiated tumors in EOpNET group and TOpNET group respectively. Furthermore, significantly higher proportion of patients in EOpNET group received surgery treatment ($P < 0.001$) than TOpNET group. The median survival period for EOpNET group was 136 (3-143) months and for TOpNET group was 85 (3-143) months ($P < 0.001$). Univariate Cox proportional hazards models were used to evaluate factors associated with survival in both groups. We found that even though gender had no effect on the survival of EOpNET group, it seems that females had a lower risk of death than males in TOpNET group (HR: 0.871, 95%CI: 0.79–0.97, $P = 0.010$). Moreover, the married people had lower risks of death than the singles in both EOpNET group (HR: 0.729, 95%CI: 0.57–0.94, $P = 0.014$) and TOpNET group (HR: 0.843, 95%CI: 0.71–1.00, $P = 0.047$). Compared to the patients diagnosed at 2004 to 2009, the patients diagnosed at 2010 to 2015 had significantly better prognosis in both EOpNET group (HR: 0.750, 95%CI: 0.59–0.96, $P = 0.020$) and TOpNET group (HR: 0.799, 95%CI: 0.71–0.89, $P < 0.001$). In relations to the T stage of pNET, we found that T2 stage patients had 3.167-fold increased death risk compared to T1 stage patients in TOpNET group (HR: 3.167, 95%CI: 2.40–4.19, $P < 0.0001$), while there was no difference in TOpNET group (HR: 1.294, 95%CI: 0.80–2.11, $P = 0.300$), and similar results were observed in patients with pathological grade II differentiation. Compared to tumors located in pancreatic head, tumors in the body (HR: 0.712, 95%CI: 0.60–0.85, $P = 0.001$) and tail (HR: 0.721, 95%CI: 0.63–0.83, $P < 0.001$) had lower risk of death in TOpNET group, while the location had no efficacy on survival in EOpNET group. Surgery reduced the risks of death in both EOpNET group (HR: 0.128, 95%CI: 0.10–0.16, $P < 0.001$) and TOpNET group (HR: 0.191, 95%CI: 0.17–0.22, $P < 0.001$) respectively.

Table 1
Characteristic distributions and survival associations by age at diagnosis among pancreatic neuroendocrine tumor (pNET) cases in SEER databa

Distributions by age at diagnosis			Survival associations by age at diagnosis				
N with data available	EOpNET (age < 50) N (%)	EOpNET (age < 50) N (%)	P values	EOpNET (age < 50) (N = 1203 ,deaths = 320)		TOpNET (age ≥ 50) (N = 4165 ,deaths = 1448)	
				HR (95%CI) P Values		HR (95%CI)	P Values
Sex	5368		0.000				
Male	586 (48.7%)	2354 (56.5%)		Reference		Reference	
Female	617 (51.3%)	1811 (43.5%)		0.808(0.65–1.01)	0.808	0.871(0.79–0.97)	0.010
Marriage	5075		0.000				
Marry	322(28.1%)	2677(68.1%)		0.729(0.57–0.94)	0.014	0.843(0.71-1.00)	0.047
Single	700(61.1%)	462(11.8%)		Reference		Reference	
Other	124(10.8%)	790(20.1%)		0.876(0.59–1.30)	0.511	1.207(1.00-1.46)	0.05
Race	5341		0.000				
Black	170(14.2%)	445(10.7%)		Reference		Reference	
White	899(75.3%)	3366(81.2%)		0.816(0.61–1.10)	0.176	0.98(0.83–1.16)	0.808
Others	125(10.5%)	336(8.1%)		0.527(0.32–0.86)	0.010	0.863(0.67–1.11)	0.250
Diagnosis years	5368		0.000				
2004–2009	448(37.2%)	1256(30.2%)		Reference		Reference	
2010–2015	755(62.8%)	2909(69.8%)		0.750(0.59–0.96)	0.020	0.799(0.71–0.89)	0.000
AJCC, 6th	3085		0.037				
I	158(23.4%)	688(28.6%)		Reference		Reference	
II	162(24.0%)	497(20.6%)		6.551(2.57–16.72)	0.000	2.219(1.71–2.89)	0.000
III	21(3.1%)	65(2.7%)		17.051(5.71–50.90)	0.000	4.871(3.31–7.17)	0.000
IV	335(49.6%)	1159(48.1%)		26.357(10.85–64.05)	0.000	8.297(6.67–10.33)	0.000
AJCC T, 6th	2712		0.316				
T1	104(19.9%)	423(16.3%)		Reference		Reference	
T2	223(36.4%)	761(36.9%)		1.294(0.80–2.11)	0.300	3.167(2.40–4.19)	0.000
T3	224(34.0%)	711(36.5%)		1.847(1.16–2.95)	0.010	3.707(2.81–4.89)	0.000
T4	62(9.7%)	204(10.3%)		3.98(2.37–6.71)	0.000	5.927(4.36–8.06)	0.000
AJCC N, 6th	2841		0.005				
N0	373(59.5%)	1453(65.6%)		Reference		Reference	
N1	254(40.5%)	761(34.4%)		1.478(1.13–1.94)	0.004	1.393(1.22–1.59)	0.000
AJCC M, 6th	3517		0.544				
M0	358 (51.7%)	1305 (53.0%)		Reference		Reference	
M1	335 (48.3%)	1159 (47.0%)		5.835(4.29–7.93)	0.000	4.831(4.22–5.53)	0.000

Distributions by age at diagnosis			Survival associations by age at diagnosis		
Differentiation	3492	0.067			
I	577 (72.2%)	1897 (70.4%)	Reference		Reference
II	162 (20.3%)	511 (19.0%)	1.299(0.81–2.10)	0.284	1.638(1.34–2.00)
III	48 (6.0%)	215 (8.0%)	6.661(4.27–10.40)	0.000	5.771(4.74–7.03)
IV	12 (1.5%)	70 (2.6%)	6.949(3.00–16.09)	0.000	6.553(4.82–8.91)
Primary site	5368	0.335			
Head	349 (29.0%)	1151 (27.6%)	Reference		Reference
Body	155 (12.9%)	581 (13.9%)	0.802 (0.53–1.22)	0.304	0.712(0.60–0.85)
Tail	388 (32.3%)	1423 (34.2%)	0.877 (0.66–1.17)	0.378	0.721(0.63–0.83)
Others	311 (25.9%)	1010 (24.2%)	1.363(1.04–1.79)	0.027	1.057(0.93–1.21)
Surgery treatment	5303	0.000			
No	393 (33.1%)	1665 (40.5%)	Reference		Reference
Yes	796 (66.9%)	2449 (59.5%)	0.128(0.10–0.16)	0.000	0.191(0.17–0.22)
Median survival time(range), months	136 (3–143)	85 (3–143)	0.000		

Totally 330 patients from Fudan University Shanghai Cancer Center (FUSCC) were pathologically diagnosed of pNETs and included in this study (Table 2), including 126 (38.2%) EOpNET patients and 204 (61.8%) TOpNET patients, respectively. The proportion of female in EOpNET group was higher than in TOpNET group, but was not statistically significant ($P = 0.362$). The ratio of tumor location (Head:body and/or tail) in pancreas of both groups were 1:1.7. Majority of patients were G1 or G2 tumors in both EOpNET group (87.0%) and TOpNET group (86.5%). Compared with SEER database, higher proportion of patients in our institution received surgery treatment in both EOpNET and TOpNET groups but was not statistically significant ($P = 0.977$). The median follow-up time in EOpNET group was 47.97 (3.6–152.83) months and in TOpNET group was 43.87 (4.33–128.67) months. G2 and G3 tumors had a 9-fold and 30-fold increased risk of death compared to G1 tumours in EOpNET group (HR: 9.437, 95%CI: 1.22–73.16, $P = 0.032$; HR: 30.44, 95%CI: 3.81–243.50, $P = 0.001$), however the risks in TOpNET group were only 1.468-fold and 4.614-fold respectively (HR: 1.468, 95%CI: 0.70–3.07, $P = 0.308$; HR: 4.614, 95%CI: 1.98–10.74, $P < 0.001$). This shows that differentiation grades play more important role in the progression of EOpNET patients. Furthermore, in accordance with the results in SEER cohort, surgery reduced the risks of death significantly in both EOpNET group (HR: 0.080, 95%CI: 0.03–0.20, $P < 0.001$) and TOpNET group (HR: 0.168, 95%CI: 0.09–0.31, $P < 0.001$).

We further analyzed the overall survival associations by age at diagnosis of pNET in the two cohorts and Kaplan Meier method and survival curves were formulated (Fig. 1). We found in SEER cohort, the overall survival in EOpNET patients was significantly better than among TOpNET patients (136 (3–143) months versus 85 (3–143) months, $P < 0.001$) with median follow-up time of 92 (3–143) months. To exclude the other causes of death of pNET patients, we analyzed according to cause specific deaths, the outcome was similar 23 (3–142) months versus 16 (3–142) months, $P < 0.001$, with median follow-up time of 18 (3–142) months. In FUSCC cohort, the overall survival in EOpNET patients was also better than TOpNET patients with median follow-up time of 39.585 (3.6–152.8) months ($N = 330$), but was not statistically significant ($P = 0.245$), maybe due to relatively small sample number.

Table 2
Characteristic distributions and survival associations by age at diagnosis among pancreatic neuroendocrine tumor (pNET) cases in FUSCC

Distributions by age at diagnosis				Survival associations by age at diagnosis			
N with data available	EOpNET (age < 50) N (%)	TOpNET (age ≥ 50) N (%)	P values	EOpNET (age < 50) (N = 126, deaths = 20)		TOpNET (age ≥ 50) (N = 204, deaths = 42)	
				HR (95%CI) P Values		HR (95%CI)	P Values
Sex	330			0.362			
Male	50(39.7%)		92(45.1%)	Reference		Reference	
Female	76(60.63%)		112(54.9%)	0.826(0.34-2.00)	0.67	0.759(0.41–1.39)	0.373
AJCC, 8th	329			0.875			
I/II	74(58.7%)		121(59.6%)	Reference		Reference	
III/IV	52(41.3%)		82(40.4%)	19.773(4.52–86.48)	0.000	6.715(3.28–13.77)	0.000
AJCC T, 8th	328			0.716			
T1	33(26.2%)		45(22.3%)	Reference		Reference	
T2	38(30.2%)		63(31.2%)	1.241(0.30–5.20)	0.768	1.194(0.42–3.36)	0.737
T3	55(43.7%)		94(46.5%)	1.656(0.464–5.907)	0.437	2.950(0.85–4.98)	0.112
AJCC N, 8th	230			0.734			
N0	75(83.3%)		119(85.0%)	Reference		Reference	
N1	15(16.7%)		21(15.0%)	3.511(0.301–41.02)	0.317	7.074(2.30-21.73)	0.001
AJCC M, 8th	330			0.902			
M0	90(71.4%)		147(72.1%)	Reference		Reference	
M1	36(28.6%)		57(27.9%)	23.270(6.62–81.83)	0.000	5.830(3.11–10.95)	0.000
Grade (WHO 2010)	323			0.936			
G1	48(39.0%)		74(37.0%)	Reference		Reference	
G2	59(48.0%)		99(49.5%)	9.437(1.22–73.16)	0.032	1.468(0.70–3.07)	0.308
G3	16(13.0%)		27(13.5%)	30.44(3.81–243.50)	0.001	4.614(1.98–10.74)	0.000
Primary site	330			0.685			
Head	46(36.5%)		70(34.3%)	Reference		Reference	
Body/ Tail	80(63.5%)		134(65.7%)	1.603(0.58–4.43)	0.363	0.945(0.50–1.78)	0.861
Surgery treatment	330			0.977			
No	19(15.1%)		31(15.2%)	Reference		Reference	
Yes	107(84.9%)		173(84.8%)	0.080(0.03–0.20)	0.000	0.168(0.09–0.31)	0.000
Median follow up time (range), months	47.97(3.6-152.83)		43.87(4.33-128.67)				

Discussion

pNETs are relatively rare tumors with an incidence of 5.25/100,000, and majority have satisfying prognosis[4]. However, they are highly heterogeneous with small percentage of patients displaying aggressive properties. For example, the overall 5-year survival in metastatic non-functional pNET was only 30%, which bring forth challenges to clinical practice[10]. Therefore, clarifying the clinical characteristics and survival associations could help greatly for the management of pNETs.

In our study, the proportion of EOpNET in FUSCC cohort (38.2%) was significantly higher than SEER cohort (28.9%). The average age at diagnosis of pNET in our cohort was 52.6 ± 12.6 years, which is earlier compared to SEER database (62 ± 15) years[4]. The mean age of diagnosis of PDAC in US is reported as 71 years, meanwhile in china is 62–65[11, 12]. Hence, it is reasonable to consider differences among different subgroups of races and the similar condition in PDAC. The overall survival of EOpNET (136 (3-143) months) was significantly better than TOpNET (85 (3-143) months) ($P < 0.001$) in SEER database, and also in the FUSCC cohort with median follow-up time of 39.585 (3.6-152.8) months ($N = 330$), though not statistically significant ($P = 0.245$), which was consistent with previous reports[9]. In this study, we analyzed both cohorts at 50 years age to keep their consistency, however this could be the reason that certain characteristics in FUSCC cohort are not consistent with or obvious as the SEER database. Therefore, exploring the reasons of different age of onset of disease in different states and races could provide new strategy for therapy in the future.

Surgery is the most effective therapy for localized tumors and even for metastatic NETs that more than 90% of liver tumors can be resected, cytoreductive surgery is recommended[2]. In our study, we found surgery can lower the risks of death significantly in both EOpNET or TOpNET group. Furthermore, the tumors located in the body and tail had lower risks of death compared to head in TOpNET patients while not in EOpNET patients. This may be associated with worsened physical status in TOpNET group as the with pancreatic head tumor patients underwent relatively more invasive surgery of pancreaticoduodenectomy.

Additionally, patients diagnosed between 2010 to 2015 had significantly better prognosis than those diagnosed between 2004 to 2009, which reflects that with earlier tumor detections due to more prevalent routine medical examinations and the systemic treatment options for pNET have also been adopted considerably in recent years. Somatostatin analogs, peptide receptor radionuclide and everolimus have been demonstrated to effectively improve the prognosis of pNET[13]. Combined chemotherapy with temozolomide and capecitabine is recently reported to prolong the progression-free survival of pNETs[14, 15]. Moreover, our study also shows unmarried patients had significantly higher death risk than the married, which coincides with previous reports suggesting that social support could potentially impact cancer survival significantly [16].

There is no consensus yet on optimal follow-up strategy for pNET. Most guidelines suggest performing enhanced CT or magnetic resonance imaging (MRI) of the abdomen yearly for the first 3 years, then every 1 to 2 years for a total of 10 years[17]. For tumors smaller than 2 cm, previous reports are controversial about observation or operation[18]. While from the perspective of our research, operation is recommended, as EOpNET group had significantly better overall survival than TOpNET.

pNETs are usually sporadic, but increasing evidences suggest the importance of genetic mutations in the initiation and development of pNETs. Jiao et al. performed whole exome sequencing in 68 sporadic pNETs and found multiple endocrine neoplasia type 1 (MEN1) and death domain-associated protein/ α -thalassemia mental retardation syndrome (DAXX/ATRX) mutations in more than 40% of pNETs. Also 14% of samples had mutations in the genes implicated in mTOR pathway[19]. Scarpa et al. performed whole genome sequencing of 102 primary pNETs and identified larger than anticipated germline contribution to clinically sporadic pNETs[3]. According to the “two-hit” hypothesis[20], gene mutation was closely associated with tumor age of onset. Therefore, future studies on the variations of genetic mutation among different age groups, especially the early-onset tumor, could help identify pNET driver genes.

The patients were all histology diagnosed in this retrospective study, hence all the patients were either from a surgical database or with positive biopsy results; thus, there may be some bias in the proportion of different stages. However, we queried the SEER database and our institution to minimize the influence of inadequate sample size and geography. Thus, the clinical characteristics of EOpNET and TOpNET and their effects on prognosis were supported and complemented by both cohorts. However, when exploring the survival associations with age at diagnosis, our database is not significant due to limitations on sample size and number of deaths. The tumor function was not distinguished, though only a small percent of pNETs were functional; this may cause the bias of prognosis, because functioning neoplasms usually have better prognosis compared to nonfunctioning tumors as a result of early diagnosis.

EOpNET constitute only 28–38% of the total pNET patients and have better prognosis, however due to young age of onset, the disease is responsible for much more of the total number of years-of-life-lost. Identifying the clinical characteristics and survival associations by age at diagnosis of pNET could help us better understand pNET, especially those early onset ones, and potentially yield strategies to delay the onset of it, or help put forward new therapeutic methods.

Conclusions

EOpNET group had significantly better overall survival than TOpNET though their clinical characteristics seem to be not significantly different, except that the proportion of female and lymph node positive status in EOpNETs was higher than in TOpNET. In the future personalized treatment of pNET, the onset age of patients will become another important factor for guiding the treatment and prognosis.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Fudan University Shanghai Cancer Center. All patients provided written informed consent.

Consent for publication

There will be no conflict of commercial interest for any of the patient with the publication of the manuscript.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

M. Liu, X. Sun and Z. Zhang contributed equally to this article, collected and analyzed the data, and drafted the manuscript. X. Xu and X. Yu reviewed and contributed to the revision of the manuscript. S. Ji and Q. Zhuo designed and reviewed the study. All authors read and approved the final manuscript.

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Figures

Figure 1
Kaplan-Meier survival curves of EOpNET and TOpNET patients in SEER database (A) all patients (B) cause specific deaths and (C) FUSCC.