Hepatobiliary & Pancreatic Diseases International 18 (2019) 538–545

Contents lists available at ScienceDirect

Hepatobiliary & Pancreatic Diseases International

journal homepage: www.elsevier.com/locate/hbpd

Original Article/Liver

Survival comparison between primary hepatic neuroendocrine neoplasms and primary pancreatic neuroendocrine neoplasms and the analysis on prognosis-related factors

Meng-Xia Li[a], Qi-Yong Li[b], Min Xiao[b], Da-Long Wan[a], Xin-Hua Chen[a], Lin Zhou[a,c], Hai-Yang Xie[a,c], Shu-Sen Zheng[a,c,*]

[a] Division of Hepatobiliary Pancreatic Surgery, First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China
[b] Division of Hepatobiliary Pancreatic Surgery, Shulan (Hangzhou) Hospital, Hangzhou 310004, China
[c] Key Laboratory of Combined Multi-organ Transplantation, Ministry of Public Health, First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China

ARTICLE INFO

Article history:
Received 6 November 2018
Accepted 29 March 2019
Available online 5 April 2019

Keywords:
Neuroendocrine neoplasms
Survival
Prognosis
Hepatic neuroendocrine neoplasms
Pancreatic neuroendocrine neoplasms

ABSTRACT

Background: Primary hepatic neuroendocrine neoplasms (PHNENs) are extremely rare and few articles have compared the prognosis of PHNENs with other neuroendocrine neoplasms (NENs). This study aimed to investigate the different prognosis between PHNENs and pancreatic NEN (PanNENs) and evaluate the relevant prognosis-related factors.

Methods: From January 2012 to October 2016, a total of 44 NENs patients were enrolled and divided into two groups according to the primary tumor location which were named group PHNENs (liver; $n=12$) and group PanNENs (pancreas; $n=32$). Demographic, clinical characteristics and survival data were compared between the two groups with Kaplan-Meier method and log-rank tests. Prognostic factors were analyzed using the Cox regression model.

Results: The overall survival of group PHNENs and group PanNENs were 25.4 ± 6.7 months and 39.8 ± 3.7 months, respectively ($P=0.037$). The cumulative survival of group PanNENs was significantly higher than that of group PHNENs ($P=0.029$). Univariate analysis revealed that sex, albumin, total bilirubin, total bile acid, aspartate aminotransferase, alkaline phosphatase, α-fetoprotein and carbohydrate antigen 19-9, histological types, treatments and primary tumor site were the prognostic factors. Further multivariate analysis indicated that albumin ($P=0.008$), histological types NEC ($P=0.035$) and treatments ($P=0.005$) were the independent prognostic factors. Based on the histological types, the cumulative survival of patients with well-differentiated neuroendocrine tumor was significant higher than that of patients with poorly differentiated neuroendocrine carcinoma in group PHNENs ($P=0.022$), but not in group PanNENs ($P>0.05$). According to the different treatments, patients who received surgery had significantly higher cumulative survival than those with conservative treatment in both groups ($P<0.05$).

Conclusions: PHNENs have lower survival compared to PanNENs. Histological types and treatments affect the prognosis. Surgical resection still remains the first line of treatment for resectable lesions and can significantly improve the survival.

© 2019 First Affiliated Hospital, Zhejiang University School of Medicine in China. Published by Elsevier B.V. All rights reserved.

Introduction

Neuroendocrine neoplasms (NENs) are a group of heterogeneous malignancies which originate from the diffused neuroendocrine system [1,2]. It was originally defined as a carcinoid tumor by Oberndorfer in 1907 [3], and the term "NENs" was officially used by World Health Organization (WHO) in 2010 [4]. The annual incidence of NENs in United States is estimated around 6.9/100 000 [5,6], which accounts for approximately 0.5% of all new malignancies. One published study [6] on the basis of data from the SEER (Surveillance, Epidemiology and End Results Program, United States) had proven that the incidence and prevalence of NENs have been increasing continuously over the past

* Corresponding author at: Division of Hepatobiliary Pancreatic Surgery, First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China.
E-mail address: shusenzheng@zju.edu.cn (S.-S. Zheng).

https://doi.org/10.1016/j.hbpd.2019.03.009
1499-3872/© 2019 First Affiliated Hospital, Zhejiang University School of Medicine in China. Published by Elsevier B.V. All rights reserved.

decades, possibly attributed to the advances of technologies which improve the diagnosis at early-stage.

Approximately 54% to 90% of the NENs originated from gastrointestinal tract, pancreas and lung [7]. Liver is the most common organ affected by metastatic NENs [8], while primary hepatic NENs (PHNENs) are rare and represent only 0.3%–4.0% of all NENs [9,10]. Several literatures analyzed the clinical characteristics, survival and relative risk factors of NENs [11–13], and most of these studies focus on gastroenteropancreatic NENs and lung NENs, while the knowledge in PHNENs is less due to the rarity. So far, very few publications are available on the differences between PHNENs and other NENs. Therefore, we conducted a retrospective study to compare the different prognosis and treatment between PHNENs and pancreatic NENs (PanNENs).

Methods

Patients

From January 2012 to October 2016, a total of 164 patients were histologically diagnosed as NENs at the First Affiliated Hospital, Zhejiang University School of Medicine, China. The primary tumor site was determined by the morphological and functional imaging including ultrasonography, upper gastrointestinal endoscopy, low gastrointestinal endoscopy, computed tomography (CT), magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT). The most common primary site was pancreas (41, 25.0%), followed by gastrointestinal tract organs (36, 22.0%) and lungs (22, 13.4%). Among these, PHNENs were only found in 12 patients (7.3%). In order to exclude the possibility of metastasis, all 12 PHNENs patients underwent all the above-mentioned examinations and were followed every 3 months. No evidence of extra-hepatic lesion was found until the patient died or the last follow-up. This study excluded those who received further treatments in non-hepatobiliary pancreatic surgical department, those with other neoplasms, and with incomplete follow-up. Totally, 45 patients were included in the analysis. Furthermore, after excluding a patient with perioperative mortality (<30 days, $n=1$), the final 44 patients were reported in this study. According to the primary tumor site, these 44 NENs patients were further subdivided into two groups: group PHNETs ($n=12$) and group PanNENs ($n=32$) (Fig. 1).

Treatment protocols

The treatments were decided according to the location, size, number of the lesions on CT and MRI [5,14,15]. In group PHNENs, if the lesions were confined within one lobe and without distant metastasis and residual liver volume exceeded 30%, liver resection (local resection and hemihepatectomy) was performed [16,17]. For patients with unresectable lesions, the conservative treatments included systemic chemotherapy, radiofrequency ablation (RFA) and transarterial chemoembolization (TACE). In group PanNENs, if the lesions were confined to pancreas with no evidence of metastasis and were resectable, a standard resection was performed based on the position of the tumor: pancreaticoduodenectomy in the presence of lesion in the head of the pancreas, distal pancreatectomy with splenectomy in the case of body-tail lesion, and total pancreatectomy in the case of diffuse lesion [14,16]. The conservative treatments included systemic chemotherapy, biotherapy with somatostatin analogs [2] or targeted therapies [2,5] [mammalian target of rapamycin (mTOR) inhibitors/vascular endothelial growth

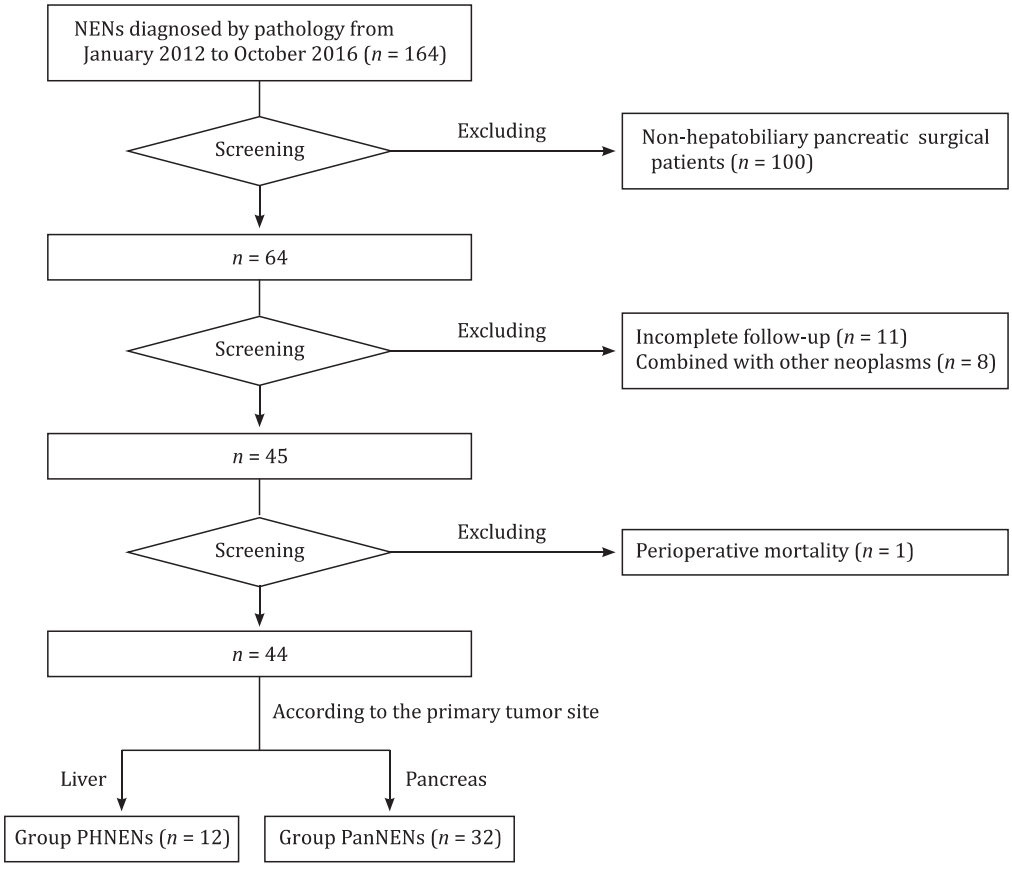

Fig. 1. Flow chart of patient selection procedures. NEN: neuroendocrine neoplasm; PHNEN: primary hepatic neuroendocrine neoplasms; PanNEN: pancreatic neuroendocrine neoplasm.

factor inhibitors]. For recurrence patients, a second operation or conservative treatment was carried out according to the principles mentioned above.

Clinical data and follow-up

All data were collected from the hospital records and the follow-up was every 3 months. Data collection included patient demographics, clinical manifestations, hemoglobin (Hb), liver functions [albumin, total bilirubin (TBil), total bile acid (TBA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP)], tumor markers [α-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), carbohydrate antigen 125 (CA125)], tumor histology, chromogranin A, treatments and patient survival. All 44 patients were regularly followed up until September 2018. Overall survival (OS) was defined as the time from the date of diagnosis to death or last follow-up.

Pathology grading standards

According to WHO classification in 2010, NENs has been classified into 3 grades based on mitotic rate and Ki-67 proliferation index: G1, mitotic rate <2 per 10 high power field (HPF) and/or Ki-67 index ≤3%; G2, mitotic rate 2–20 per 10 HPF and/or Ki-67 index 3%–20%; G3, mitotic rate >20 per 10 HPF and/or Ki-67 index >20% [18,19]. NENs were defined as three main types: (a) well-differentiated neuroendocrine tumor (NET). This type is subdivided into NET G1 and NET G2 which are low grade and intermediate grade NEN respectively; (b) poorly differentiated neuroendocrine carcinoma (NEC), which is high grade NEN (G3); and (c) mixed adenoendocrine carcinoma (MANEC) including two components (adenocarcinoma and NENs) [4].

Statistical analysis

Statistical analysis was performed using SPSS 22.0. Variables were expressed as frequency, means and standard deviations, or medians and interquartile ranges. The Mann–Whitney and Pearson Chi-square tests (or Fisher exact test) were used to calculate the statistical significance of the demographical and clinical variables. The cumulative survival rate was analyzed by Kaplan-Meier survival curve and log-rank test. By using Cox regression model, variables with $P < 0.05$ in univariate analysis were included in multivariate analysis to further analyze the independent prognostic factors. A P value <0.05 was considered statistically significant.

Results

Baseline demographical and clinical characteristics

The median follow-up time for PHNENs patients was 18.4 months (1.8–65.4) and for PanNEN patients was 34.1 months (8.1–77.7). During follow-up, 17 patients died (7 patients of NET and 10 patients of NEC) and the rest of patients were still alive for more than 24 months. No patient had a history of hepatitis or liver cirrhosis in group PHNENs, and only 2 patients had hepatitis B surface antigen positive in group PanNENs. Twenty-three patients (52.3%) had no obvious clinical symptoms. Among the remaining 21 patients, abdominal pain was the most common symptom (10, 47.6%). Other nonspecific symptoms were jaundice (4, 19.0%), fatigue (3, 14.3%), abdominal distension (2, 9.5%), nausea or vomiting (1, 4.8%), and weight loss (1, 4.8%). None of the patients manifested as hormonal hypersecretion related symptoms, such as flushing, diarrhea, palpitation, hypoglycemia, etc.

The mean age of patients at the time of diagnosis was 55.9 years and 56.7 years in group PHNENs and group PanNENs, respectively. Compared with group PanNENs, group PHNENs was more frequently presented with larger tumor size (8.0 vs. 4.4 cm; $P = 0.001$) and high level of TBil, TBA, ALP and CA125. Of the 12 PHNENs patients, 7 were NEC and 5 were NET G2; of the 32 PanNENs patients, 11 were NEC, 3 were NET G1 and 18 were NET G2. NEC accounted for a larger proportion of NENs in group PHNENs than that in group PanNENs, but the difference was not statistically significant (58.3% vs. 34.4%; $P = 0.155$). Besides, no patient diagnosed with MANEC. The two groups were comparable in other clinicopathological characteristics, including age, sex, other liver functions and tumor markers, and positive rate of chromogranin A. The remaining baseline characteristics of the two groups are shown in Table 1.

Treatments

More surgeries were performed in patients with PanNENs than patients with PHNENs (68.8% vs. 50.0%; $P = 0.255$, Table 1), while the remaining 16 patients were conservatively treated. In group PHNENs, 4 patients underwent local resection, 2 underwent hemihepatectomy; 1 received RFA, 2 received TACE and 3 received

Table 1
Baseline characteristics of group PHNENs and group PanNENs.

Characteristics	PHNENs ($n = 12$)	PanNENs ($n = 32$)	P value
Age (yr)	55.9 ± 13.0	56.7 ± 11.2	0.752
Male/female	7/5	16/16	0.626
Hemoglobin (g/L)	125.7 ± 13.3	128.9 ± 21.6	0.323
Albumin (g/L)	42.2 ± 7.0	43.1 ± 3.6	0.989
TBil (μmol/L)	11.5 (10.0–42.3)	9.0 (6.3–13.8)	**0.042**
TBA (μmol/L)	12.0 (6.8–21.8)	4.0 (3.0–6.8)	**<0.001**
ALT (U/L)	24.0 (14.0–79.0)	19.5 (12.8–28.0)	0.391
AST (U/L)	30.0 (18.3–92.5)	21.0 (17.0–25.8)	0.104
ALP (U/L)	105.0 (74.8–332.0)	67.5 (56.0–91.3)	**0.006**
AFP (ng/mL)	2.6 (2.0–4.6)	3.0 (2.3–5.6)	0.285
CEA (ng/mL)	2.6 (1.7–8.0)	2.3 (1.5–4.1)	0.742
CA19-9 (U/mL)	10.6 (5.7–78.2)	10.8 (4.6 – 25.6)	0.571
CA125 (U/mL)	21.2 (15.3–23.2)	9.6 (6.6–13.7)	**0.023**
Tumor size (cm)	8.0 ± 3.4	4.4 ± 2.6	**0.001**
Histological types (NET/NEC)	5/7	21/11	0.155
Chromogranin A (+/−)	12/0	24/8	0.058
Surgery/non-surgery	6/6	22/10	0.255

TBil: total bilirubin; TBA: total bile acid; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; AFP: α-fetoprotein; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; CA125: carbohydrate antigen 125; NET: neuroendocrine tumor; NEC: neuroendocrine carcinoma.

Table 2
Biochemistry and hematological parameters after treatment.

Variables	PHNENs ($n=12$)	PanNENs ($n=32$)	P value
One month after treatment			
Hemoglobin (g/L)	115.8 ± 11.9	117.7 ± 20.6	0.668
Albumin (g/L)	40.0 ± 6.3	40.6 ± 5.7	0.836
TBil (μmol/L)	14.5 (8.1–38.3)	9.0 (7.0–12.0)	0.053
TBA (μmol/L)	10.0 (8.0–19.8)	4.0 (3.0–5.3)	**<0.001**
ALT (U/L)	38.0 (18.8–76.0)	31.0 (13.3–52.5)	0.352
AST (U/L)	33.5 (23.5–56.8)	24.0 (15.0–40.6)	0.063
ALP (U/L)	132.0 (82.0–379.0)	95.0 (69.5–148.8)	0.151
AFP (ng/mL)	2.3 (1.5–6.7)	3.7 (2.6–4.7)	0.301
CEA (ng/mL)	2.8 (1.2–31.2)	1.5 (1.0–2.9)	0.157
CA19-9 (U/mL)	15.2 (4.0–36.1)	5.1 (2.2–10.1)	0.142
CA125 (U/mL)	36.8 (17.1–47.0)	18.7 (8.6–65.3)	0.699
Six months after treatment			
Hemoglobin (g/L)	110.5 ± 20.7	123.8 ± 25.2	0.132
Albumin (g/L)	43.2 ± 4.4	43.4 ± 5.8	0.889
TBil (μmol/L)	11.5 (9.8–14.3)	8.0 (7.0–9.0)	**0.017**
TBA (μmol/L)	6.5 (3.8–10.3)	4.5 (3.0–6.0)	0.297
ALT (U/L)	25.0 (18.3–30.5)	18.0 (14.5–40.5)	0.725
AST (U/L)	34.0 (24.3–49.5)	26.0 (18.5–33.5)	0.123
ALP (U/L)	112.5 (48.0–311.5)	76.0 (63.0–123.0)	0.575
AFP (ng/mL)	3.3 (2.0–1289.7)	3.8 (2.6–5.7)	0.665
CEA (ng/mL)	1.9 (0.9–5.3)	2.3 (1.5–3.9)	0.300
CA19-9 (U/mL)	13.3 (9.3–122.5)	10.7 (3.4–24.6)	0.182
CA125 (U/mL)	19.5 (10.8–31.9)	12.4 (8.6–22.6)	0.327

TBil: total bilirubin; TBA: total bile acid; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; AFP: α-fetoprotein; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; CA125: carbohydrate antigen 125.

systemic chemotherapy. In group PanNENs, 3 patients underwent pancreaticoduodenectomy, 17 underwent distal pancreatectomy and 2 underwent total pancreatectomy; the remaining 10 patients received systemic chemotherapy, 2 of them received biotherapy together and 2 of them received novel targeted therapies together. Postoperative pancreatic leakage occurred in 7 patients and was cured by conservative treatments. Other parameters, except TBil and TBA, had no significant difference between the two groups, neither one-month nor 6-month after the treatment (Table 2).

Survival data

The OS in group PHNENs was 25.4 ± 6.7 months and that in group PanNENs was 39.8 ± 3.7 months ($P=0.037$). There was significant difference in the 1-year survival rate between group PHNENs and group PanNENs (66.7% vs. 93.8%; $P=0.039$). The cumulative survival of group PanNENs was significantly higher than that of group PHNENs ($P=0.029$, Fig. 2). The 2-year recurrence rates were 50.0% (3/6) and 68.2% (15/22) in group PHNENs and group PanNENs respectively ($P=0.731$). According to the principle of treatments mentioned above, those recurrent patients received appropriate treatments.

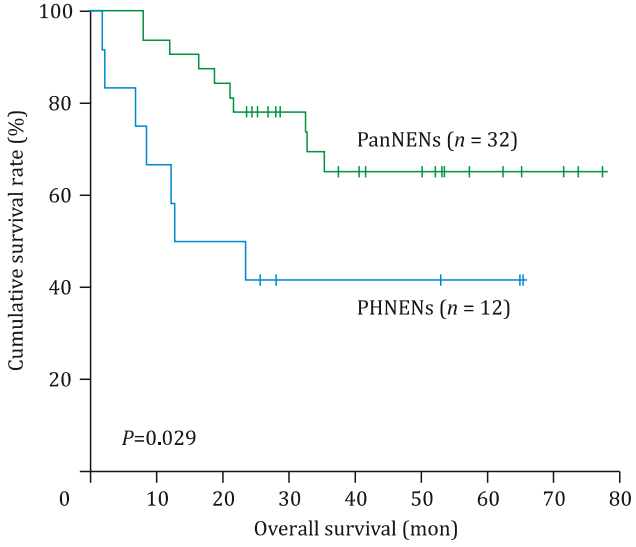

Fig. 2. The cumulative survival of patients in group PHNENs and group PanNENs. PHNEN: primary hepatic neuroendocrine neoplasms; PanNEN: pancreatic neuroendocrine neoplasm.

Univariate and multivariate analyses

Univariate analysis showed that the prognostic risk factors were female, low serum albumin level (≤35 g/L), high level of TBil (>21 μmol/L), TBA (>12 μmol/L), AST (>40 U/L), ALP (>150 U/L), AFP (>20 ng/mL) and CA19-9 (>37 U/mL), histological types (NEC), treatments (non-surgery) and primary tumor site (liver). To these factors, multivariate analysis further indicated that the serum albumin level (≤35 g/L; HR: 40.004, 95% CI = 2.583–619.622, $P=0.008$), histological types (NEC; HR: 25.363, 95% CI=1.248–515.632, $P=0.035$) and treatments (surgery; HR: 0.021, 95% CI = 0.001–0.320, $P=0.005$) were the prognostic factors (Table 3).

Based on the histological type, the patients in each group were further divided into two subgroups, subgroup NET and NEC, respectively. In group PHNENs, the cumulative survival rate of patients with NET was significant higher than that of patients with NEC ($P=0.022$, Fig. 3A). Whereas, the difference was not found in group PanNENs ($P=0.497$, Fig. 3B). Furthermore, according to the different treatments, the two groups were respectively reorganized into two subgroups, subgroup surgery and non-surgery (conservative). Patients who received surgery showed significantly higher cumulative survival than conservative treatment in group PHNENs ($P=0.003$, Fig. 3C) and group PanNENs ($P=0.022$, Fig. 3D).

Discussion

NENs are relatively rare neoplasms that are rich in neuroendocrine cells and can arise in any anatomical site, mainly

Table 3
Predictors of survival by univariate and multivariate analysis.

Variables	Univariate analysis				Multivariate analysis			
	Wald	Hazard ratio	95% CI	*P* value	Wald	Hazard ratio	95% CI	*P* value
Age (>50 year)	0.040	0.899	0.317–2.555	0.842	–	–	–	–
Sex (female)	4.375	3.060	1.073–8.728	**0.036**	3.007	13.388	0.713–251.303	0.083
Hemoglobin (≤110 g/L)	2.839	2.456	0.864–6.984	0.092	–	–	–	–
Albumin (≤35 g/L)	15.439	18.571	4.324–79.752	**<0.001**	6.963	40.004	2.583–619.622	**0.008**
TBil (>21 μmol/L)	11.491	7.000	2.272–21.562	**0.001**	2.418	23.381	0.440–1242.388	0.120
TBA (>12 μmol/L)	6.488	3.682	1.350–10.041	**0.011**	1.477	7.811	0.284–214.868	0.224
ALT (>35 U/L)	3.197	2.488	0.916–6.755	0.074	–	–	–	–
AST (>40 U/L)	10.906	5.336	1.975–14.415	**0.001**	0.025	0.804	0.054–12.075	0.875
ALP (>150 U/L)	13.860	8.791	2.799–27.608	**< 0.001**	1.019	0.085	0.001–10.214	0.313
AFP (>20 ng/mL)	5.564	3.909	1.259–12.131	**0.018**	2.432	2.920	0.759–11.227	0.119
CEA (>5 ng/mL)	0.159	1.257	0.407–3.883	0.690	–	–	–	–
CA19-9 (>37 U/mL)	6.351	3.675	1.336–10.115	**0.012**	1.110	2.863	0.405–20.257	0.292
CA125 (>35 U/mL)	1.485	2.517	0.570–11.116	0.223	–	–	–	–
Tumor size (>5 cm)	1.330	1.824	0.657–5.068	0.249	–	–	–	–
Histological types (NEC)	4.682	2.919	1.106–7.704	**0.030**	4.426	25.363	1.248–515.632	**0.035**
Treatments (surgery)	12.134	0.155	0.054–0.443	**<0.001**	7.729	0.021	0.001–0.320	**0.005**
Primary tumor site (liver)	4.342	2.809	1.063–7.423	**0.037**	1.174	0.169	0.007–4.222	0.279

95% CI: 95% confidence interval; TBil: total bilirubin; TBA: total bile acid; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; AFP: α-fetoprotein; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; CA125: carbohydrate antigen 125; NEC: neuroendocrine carcinoma.

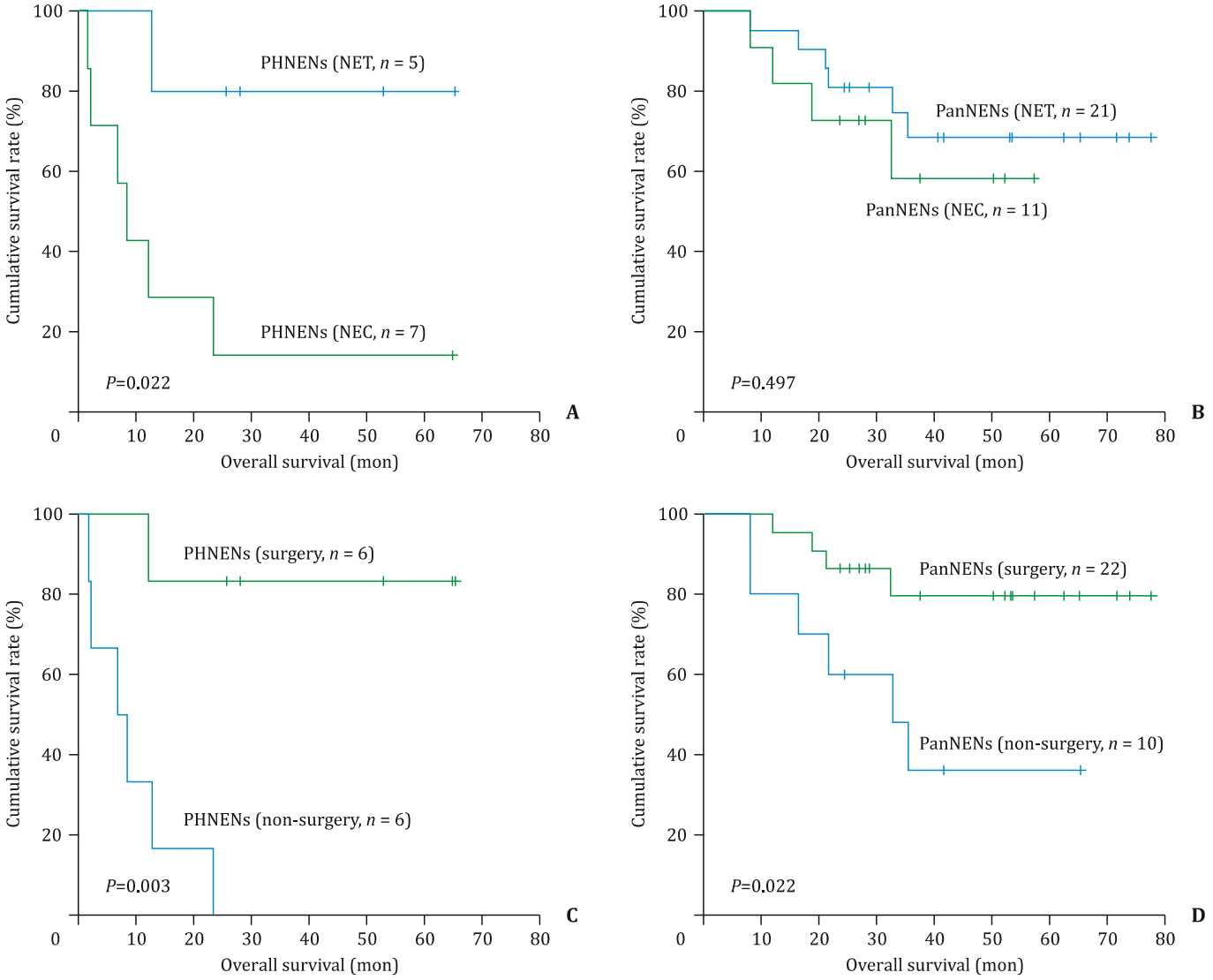

Fig. 3. The cumulative survival of patients with neuroendocrine tumors (NET) and of patients with neuroendocrine carcinomas (NEC) in group PHNENs (**A**) and group PanNENs (**B**). The cumulative survival of patients with surgery and without surgery in group PHNENs (**C**) and Group PanNENs (**D**). PHNEN: primary hepatic neuroendocrine neoplasms; PanNEN: pancreatic neuroendocrine neoplasm.

arising from digestive tract and lung [20]. According to whether the symptoms caused by hormones, NENs can be classified as functional and non-functional tumors [21]. The majority of NENs are non-functional and the clinical manifestations are mostly non-specific [22]. Our study showed the most common locations of primary tumor were pancreas, gastrointestinal tract and lung. More than half of the patients were asymptomatic and the rest of the patients mainly presented with abdominal pain while no patient manifested as hormone-related syndrome. The results were consistent with the previous study [23]. Interestingly, the incidence of PHNENs in our hospital was significantly higher than that in literature (7.3% vs. 0.3%–4.0%) which may be attributed to the increased prevalence of PHNENs in recent years. Currently, combination of morphological and functional imaging methods is helpful to preoperative diagnosis of PHNENs, but the final diagnosis depends on pathology. Thirty-six of 44 (81.8%) patients in our study showed immunopositivity for chromogranin A which is a valuable biomarker for pathological diagnosis and to monitor NENs [24,25].

Up to now, as compared with other NENs, a limited number of studies have been reported on PHNENs given the lower incidence. Lv et al. reported that the patients with PHNENs seemed to achieve long-term survival than secondary HNENs [26]. To our knowledge, comparative study of PHNENs and other NENs has never been reported. In this study, we investigated the clinical characteristics and outcomes of the patients who were diagnosed with PHNENs or PanNENs. Patients in group PHNENs had larger tumor size and worse liver function than those in group PanNENs. There were several reasons for this result: (1) liver is the largest internal organ and provides more space for tumor growth; (2) NENs usually grow slowly, which are concealed and difficult to discover in the early stages; (3) abnormal liver function is more likely to occur when liver parenchyma is destroyed directly by tumor. Considering these points, the patients with PHNENs may have been in the liver for a long time before diagnosis.

In the present study, we found that the OS of group PHNENs was significantly shorter than that of group PanNENs. Several factors may influence the survival of NENs [27]. Boyar et al. performed a retrospective study and demonstrated that the primary tumor site was one of outcome predictors in NENs patients [28]. Jiao et al. found that the survival rate of patients with PanNENs was better than those with gastroenteric NENs [29]. To investigate the reasons for survival differences between the two groups, we performed univariate and multivariate analysis using Cox regression model and the results revealed that serum albumin level, histological types and treatments were all important predictors of outcome.

As ever mentioned by the previous studies [22,30], histological grading is a key factor of the prognosis. According to WHO 2010 classification standard, NEC indicated a notable correlation with poor survival. Recently, 28 PHNENs patients were reported by Chen et al. and they figured out that high expression of Ki-67 was an independent prognostic factor [10]. Shi et al. made a retrospective study of 22 PHNENs patients who had received surgical resections [31]. Their study also indicated that lower cellular proliferation grade (G1/G2) was a favorable prognostic factor for PHNENs, which was similar with our results. In group PHNENs, the difference in cumulative survival was significant between the patients with NET and those with NEC. In group PanNENs, a trend towards higher cumulative survival of patients with NET compared to those with NEC was found, although the difference was not statistically significant. These results supported the importance of histological type to predict the prognosis.

To date, surgical resection remains the preferable treatment for NENs, which is considered the only possible cure for the disease. In our study, a total of 28 patients received radical surgery and the cumulative survival of the patients with surgery was significant higher than that of the patients with conservative treatment in both group PHNENs and group PanNENs. Many research findings confirmed the importance of surgical resection on survival [14,32] and the postoperative 5-year survival rate is up to 80% [33–35]. Moreover, Zhou et al. performed a meta-analysis and demonstrated that the palliative resection of the primary tumor in PanNENs patients with unresectable liver metastases increases survival [36]. The study further proved the effect of the radical and palliative surgery. In addition, a study conducted by Fang et al. showed that patients with NETs or NECs both benefit from surgery [32]. In our study, one of the NEC patients in group PHNENs received radical resection and survived for 64.9 months without recurrence. Although the tumor histological type was poor, the long-term survival after surgery is proven to be satisfactory. Currently, there is no robust evidence to testify the effect of surgery for NET better than for NEC [37]. Besides, organ transplantation remains controversial as an ideal treatment due to donors shortage and high recurrence rates [38,39]. In summary, for NENs (either NET or NEC), surgical resection is the first choice if conditions are suitable. Surgery could be performed safely and effectively with low incidence of postoperative serious complications.

The conservative treatments could improve the prognosis of patients with unresectable NENs [40]. The systemic therapies for unresectable NENs consist of biotherapy with somatostatin analogues, targeted therapies with mTOR and tyrosine-kinase inhibitors [5], peptide receptor radionuclide therapy [41] and chemotherapy. For PHNENs, TACE as the liver-directed intra-arterial therapy has been used to relieve the tumor burden. Localized-ablative techniques (RFA, microwave, laser ablation) could also be used in unresectable or recurrent liver lesions with diameter less than 5 cm [5]. Faggiano et al. summarized that all available non-surgical treatments for NENs are generally well tolerated and they suggested that chemotherapy should be considered after other therapeutic lines because that the cumulative toxicities is likely to increase the incidence of adverse events [2].

Serum albumin is synthesized in the liver and represents both hepatic synthetic function and nutritional status [42]. Low serum albumin level may occur in the following situations: less synthesis, high consumption and excess excretion. In recent years, the prognostic value of serum albumin level has been studied in various diseases and these results indicated that pretreatment serum albumin level could affect survival in cancerous patients [43–45]. Similarly, our data showed that a low serum albumin level ($\leq$35 g/L) is an indicator of shorter OS and the results hint that intensive nutritional support may be necessary. As a modifiable risk factor, the serum albumin level could potentially be improved with nutritional supplementation. However, only a few patients presented with low serum albumin level and they were mainly in group PHNENs, thus the conclusion requires further investigation.

Our study had several limitations. Firstly, it was a retrospective study and recall bias may happen. Secondly, somatostatin receptor scintigraphy and 68 Gallium PET/CT are highly sensitive methods to detect primary site of NENs. Unfortunately, due to limited resources in China, our hospital does not have the equipment and sufficient techniques to perform the examinations. Therefore, we were not able to provide any related data. Thirdly, our study only involved a small sample size from a single center and the follow-up period was relatively short. In order to further investigate the differences between PHNENs and PanNENs, we plan to continue follow-up on these patients and include more PHNENs cases into future study. More clinical studies will also be performed in multicenter to obtain more samples to solidify the conclusion of our study.

In conclusion, PHNENs patients have lower survival rate compared to PanNENs. Histological types, serum albumin level and

treatments affect the prognosis. The outcome of NET is better than NEC. Surgical resection is still the main option of treatment for resectable lesions and can significantly improve the survival of PH-NENs and PanNENs patients.

Acknowledgment

We thank for the proofreading by Dr. James Swanson, Liberty University, USA.

Contributors

LMX proposed the study. LMX and LQY performed the research and wrote the first draft. XM, WDL, CXH, ZL and XHY collected and analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. LMX and LQY contributed equally to the article. ZSS is the guarantor.

Funding

This study was supported by grants from Medical and Health Scientific Research Foundation Program of Zhejiang Province (2010KYB047), Innovative Research Groups of National Natural Science Foundation of China (81721091), and National S&T Major Project of China (2018ZX10301201).

Ethical approval

This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

[1] Burad DK, Kodiatte TA, Rajeeb SM, Goel A, Eapen CE, Ramakrishna B. Neuroendocrine neoplasms of liver – a 5-year retrospective clinico-pathological study applying World Health Organization 2010 classification. World J Gastroenterol 2016;22:8956–8966.
[2] Faggiano A, Lo Calzo F, Pizza G, Modica R, Colao A. The safety of available treatments options for neuroendocrine tumors. Expert Opin Drug Saf 2017;16:1149–1161.
[3] Caplin ME, Buscombe JR, Hilson AJ, Jones AL, Watkinson AF, Burroughs AK. Carcinoid tumour. Lancet 1998;352:799–805.
[4] Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumors of the digestive system. 4th ed. Lyon: IARC Press; 2010.
[5] Uri I, Avniel-Polak S, Gross DJ, Grozinsky-Glasberg S. Update in the therapy of advanced neuroendocrine tumors. Curr Treat Options Oncol 2017;18:72.
[6] Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol 2017;3:1335–1342.
[7] Camargo ÉS, Viveiros Mde M, Corrêa Neto IJ, Robles L, Rezende MB. Primary hepatic carcinoid tumor: case report and literature review. Einstein (Sao Paulo) 2014;12:505–508.
[8] Pathak S, Dash I, Taylor MR, Poston GJ. The surgical management of neuroendocrine tumour hepatic metastases. Eur J Surg Oncol 2013;39:224–228.
[9] Parkash O, Ayub A, Naeem B, Najam S, Ahmed Z, Jafri W, et al. Primary hepatic carcinoid tumor with poor outcome. J Coll Physicians Surg Pak 2016;26:227–229.
[10] Chen RW, Qiu MJ, Chen Y, Zhang T, He XX, Li Y, et al. Analysis of the clinicopathological features and prognostic factors of primary hepatic neuroendocrine tumors. Oncol Lett 2018;15:8604–8610.
[11] Ito T, Tanaka M, Sasano H, Osamura YR, Sasaki I, Kimura W, et al. Preliminary results of a Japanese nationwide survey of neuroendocrine gastrointestinal tumors. J Gastroenterol 2007;42:497–500.
[12] Juchems M. Neuroendocrine tumors of the abdomen. Radiologe 2018;58:36–44.
[13] Cao LL, Lu J, Lin JX, Zheng CH, Li P, Xie JW, et al. Incidence and survival trends for gastric neuroendocrine neoplasms: an analysis of 3523 patients in the SEER database. Eur J Surg Oncol 2018;44:1628–1633.
[14] Tamburrino D, Spoletini G, Partelli S, Muffatti F, Adamenko O, Crippa S, et al. Surgical management of neuroendocrine tumors. Best Pract Res Clin Endocrinol Metab 2016;30:93–102.
[15] Song JE, Kim BS, Lee CH. Primary hepatic neuroendocrine tumor: a case report and literature review. World J Clin Cases 2016;4:243–247.
[16] Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut 2012;61:6–32.
[17] Guglielmi A, Ruzzenente A, Conci S, Valdegamberi A, Iacono C. How much remnant is enough in liver resection? Dig Surg 2012;29:6–17.
[18] Wang LX, Liu K, Lin GW, Jiang T. Primary hepatic neuroendocrine tumors: comparing CT and MRI features with pathology. Cancer Imaging 2015;15:13.
[19] Citterio D, Pusceddu S, Facciorusso A, Coppa J, Milione M, Buzzoni R, et al. Primary tumour resection may improve survival in functional well-differentiated neuroendocrine tumours metastatic to the liver. Eur J Surg Oncol 2017;43:380–387.
[20] Chung C. Management of neuroendocrine tumors. Am J Health Syst Pharm 2016;73:1729–1744.
[21] Kulke MH, Shah MH, Benson AB 3rd, Bergsland E, Berlin JD, Blaszkowsky LS, et al. Neuroendocrine tumors, version 1.2015. J Natl Compr Canc Netw 2015;13:78–108.
[22] Zhang M, Zhao P, Shi X, Zhao A, Zhang L, Zhou L. Clinicopathological features and prognosis of gastroenteropancreatic neuroendocrine neoplasms in a Chinese population: a large, retrospective single-centre study. BMC Endocr Disord 2017;17:39.
[23] Fottner C, Ferrata M, Weber MM. Hormone secreting gastro-entero-pancreatic neuroendocrine neoplasias (GEP-NEN): when to consider, how to diagnose? Rev Endocr Metab Disord 2017;18:393–410.
[24] Marotta V, Zatelli MC, Sciammarella C, Ambrosio MR, Bondanelli M, Colao A, et al. Chromogranin A as circulating marker for diagnosis and management of neuroendocrine neoplasms: more flaws than fame. Endocr Relat Cancer 2018;25:R11–R29.
[25] Kruljac I, Vurnek I, Maasberg S, Kust D, Blaslov K, Ladika Davidović B, et al. A score derived from routine biochemical parameters increases the diagnostic accuracy of chromogranin A in detecting patients with neuroendocrine neoplasms. Endocrine 2018;60:395–406.
[26] Lv Y, Huang C, Xu H, Han X, Zhang L, Mao W, et al. Clinicopathological characteristics of the primary and metastatic hepatic neuroendocrine tumors and the relevant prognosis-related factors: a retrospective study of 81 cases in a single Chinese center. J Cancer 2018;9:479–487.
[27] Leoncini E, Carioli G, La Vecchia C, Boccia S, Rindi G. Risk factors for neuroendocrine neoplasms: a systematic review and meta-analysis. Ann Oncol 2016;27:68–81.
[28] Boyar Cetinkaya R, Aagnes B, Myklebust TÅ, Thiis-Evensen E. Survival in neuroendocrine neoplasms: a report from a large Norwegian population-based study. Int J Cancer 2018;142:1139–1147.
[29] Jiao X, Li Y, Wang H, Liu S, Zhang D, Zhou Y. Clinicopathological features and survival analysis of gastroenteropancreatic neuroendocrine neoplasms: a retrospective study in a single center of China. Chin J Cancer Res 2015;27:258–266.
[30] Nomura Y, Nakashima O, Akiba J, Ogasawara S, Fukutomi S, Yamaguchi R, et al. Clinicopathological features of neoplasms with neuroendocrine differentiation occurring in the liver. J Clin Pathol 2017;70:563–570.
[31] Shi C, Zhao Q, Dai B, Xie F, Yang J. Primary hepatic neuroendocrine neoplasm: long-time surgical outcome and prognosis. Medicine (Baltimore) 2018;97:e11764.
[32] Fang C, Wang W, Zhang Y, Feng X, Sun J, Zeng Y, et al. Clinicopathologic characteristics and prognosis of gastroenteropancreatic neuroendocrine neoplasms: a multicenter study in South China. Chin J Cancer 2017;36:51.
[33] Zhang A, Xiang J, Zhang M, Zheng S. Primary hepatic carcinoid tumours: clinical features with an emphasis on carcinoid syndrome and recurrence. J Int Med Res 2008;36:848–859.
[34] Knox CD, Anderson CD, Lamps LW, Adkins RB, Pinson CW. Long-term survival after resection for primary hepatic carcinoid tumor. Ann Surg Oncol 2003;10:1171–1175.
[35] Li W, Zhuang BW, Wang Z, Liao B, Hong LY, Xu M, et al. Case report of contrast-enhanced ultrasound features of primary hepatic neuroendocrine tumor: a CARE-compliant article. Medicine (Baltimore) 2016;95:e3450.
[36] Zhou B, Zhan C, Ding Y, Yan S, Zheng S. Role of palliative resection of the primary pancreatic neuroendocrine tumor in patients with unresectable metastatic liver disease: a systematic review and meta-analysis. Onco Targets Ther 2018;11:975–982.
[37] Frilling A, Clift AK. Surgical approaches to the management of neuroendocrine liver metastases. Endocrinol Metab Clin North Am 2018;47:627–643.
[38] Moris D, Tsilimigras DI, Ntanasis-Stathopoulos I, Beal EW, Felekouras E, Vernadakis S, et al. Liver transplantation in patients with liver metastases from neuroendocrine tumors: a systematic review. Surgery 2017;162:525–536.
[39] Clift AK, Frilling A. Liver transplantation and multivisceral transplantation in the management of patients with advanced neuroendocrine tumours. World J Gastroenterol 2018;24:2152–2162.

[40] Ioachimescu AG. Management of neuroendocrine tumors in the twenty-first century. Endocrinol Metab Clin North Am 2018;47:xiii–xxiv.
[41] Severi S, Grassi I, Nicolini S, Sansovini M, Bongiovanni A, Paganelli G. Peptide receptor radionuclide therapy in the management of gastrointestinal neuroendocrine tumors: efficacy profile, safety, and quality of life. Onco Targets Ther 2017;10:551–557.
[42] Shen J, Wen T, Li C, Yan L, Li B, Yang J. The prognostic prediction role of preoperative serum albumin level in patients with intahepatic cholangiocarcinoma following hepatectomy. Dig Dis 2018;36:306–313.
[43] Go SI, Jeon H, Park SW, Kang MH, Kim HG, Lee GW. Low pre-treatment nutritional index is significantly related to poor outcomes in small cell lung cancer. Thorac Cancer 2018;9:1483–1491.
[44] Liu J, Wang F, Li S, Huang W, Jia Y, Wei C. The prognostic significance of preoperative serum albumin in urothelial carcinoma: a systematic review and meta–analysis. Biosci Rep 2018;38.
[45] Li J, Cheng Y, Liu G, Ji Z. The association of pretreatment serum albumin with outcomes in bladder cancer: a meta-analysis. Onco Targets Ther 2018;11:3449–3459.