Medicine®

OPEN

Effects of tumor origins and therapeutic options on the prognosis of hepatic neuroendocrine tumors
A retrospective study

Xiaoxiao Jiao, BS[a] , Wenqing Luan, BS[b], Xiaoqian Peng, BS[a], Lu Liu, BS[a], Lianfeng Zhang, MD, PhD[a], Lin Zhou, MD, PhD[a],*

Abstract

Hepatic neuroendocrine tumors (HNETs) are uncommon neoplasms that can be subdivided into 2 types: primary and metastatic HNETs. Due to its rarity, heterogeneity and complexity, the diagnosis, treatment modalities and prognosis are still controversial.

This retrospective study reviewed the effects of tumor origins and therapeutic options on the prognosis of gastroenteropancreatic neuroendocrine tumors with liver metastasis (GEP-NETLM) and primary hepatic neuroendocrine tumors (PHNETs), providing additional evidence for clinicians evaluating patients.

HNETs consisted of PHNETs and GEP-NETLM. GEP-NETLM (76.2%, 112/147) was more common, which was mainly manifested as multiple lesions in both lobes of the liver. PHNETs were relatively rare (23.8%, 35/147) and were mainly single lesion located in the right lobe of the liver. In patients with GEP-NETLM, primary tumor resection could prolong survival ($P = .044$). As the most widely used treatment method, systematic therapy alone could not achieve a satisfactory survival. However, the combination with hepatectomy or liver-directed therapy improved the prognosis ($P = .023$). As the main treatment, patients with PHNETs treated with local therapy could achieve a better prognosis ($P = .049$). Compared with PHNETs patients, GEP-NETLM patients with higher ki-67 index showed higher mortality and poorer prognosis ($P = .006$).

Therefore, patients with PHNETs can be distinguished from GEP-NETLM by comprehensive imaging examinations and long-term follow-ups. The choice of appropriate treatment strategies can improve the prognosis of HNETs patients.

Abbreviations: AFP = alpha fetoprotein, CA19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, CgA = chromogranin, GEP-NETLM = gastroenteropancreatic neuroendocrine tumors with liver metastasis, HBsAg = hepatitis B virus surface antigen, HNETs = hepatic neuroendocrine tumors, MANEC = mixed adenoendocrine carcinoma, NEC = neuroendocrine carcinoma, NET = neuroendocrine tumor, NSE = neuron-specific enolase, OS = overall survival, PHNETs = primary hepatic neuroendocrine tumors, RFA = radiofrequency thermal ablation, Syn = synaptophysin, TAE/ TACE = transarterial embolization / transarterial chemoembolization.

Keywords: liver, neuroendocrine tumors, primary, prognosis, treatment

1. Introduction

Neuroendocrine tumors (NETs) originate from enterochromaffin cells, and encompass a heterogeneous group that has a broad spectrum of clinical behavior, up to 55% of these tumors occur in the gastrointestinal tract.[1,2] Due to vague clinical symptoms and convert onsets, approximately 12.9% of patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are diagnosed with distant metastases.[3,4] Apart from regional lymph nodes, the liver is the predominant metastatic site, while it is an uncommon site for the origin of NETs.[5] Primary hepatic neuroendocrine tumors (PHNETs) are extremely rare and account for approximatively 0.3% of all NETs and 0.28% to 0.46% of liver malignancies, yet the incidence shows a rising trend in recent years.[6,7] As slow-growing tumors with indolent disease courses, PHNETs show better prognosis compared with primary hepatic carcinoma. Since the first description of PHNETs by Edmondson in 1958,[7] the early diagnosis is still a problem worthy of discussion.

The similarity in unknown primary sites between the pathological and imaging features of PHNETs and gastroenteropancreatic neuroendocrine tumors with liver metastasis (GEP-NETLM), makes their differential diagnosis difficult. Meanwhile, due to the rarity, heterogeneity, and variable symptomatology of hepatic neuroendocrine tumors (HNETs),

the selection of treatment strategies and the influencing factors of prognosis are not clear. In this study, we report our institutions experience in HNETs management and confirm the potential prognostic factors, which might provide a better clinical understanding of HNETs to promote the therapeutic outcomes.

2. Methods

2.1. Patients

A total of 640 patients with pathologically diagnosed GEP-NETs who presented at the First Affiliated Hospital of Zhengzhou University between January 2010 and December 2017 were enrolled in this study. Among these, 147 patients with pathologically confirmed HNETs (PHNETs and GEP-NETLM) were included in the retrospective analysis. The study was approved by the hospitals Ethics Committee, and informed consent was obtained from all patients.

The diagnostic criteria of PHNETs were as follows:

1. diagnosed as HNETs by pathological morphology and immunohistochemical assessment;
2. located within the hepatic parenchyma and separated from the other organs;
3. unaccompanied by other lesions of hepatic tumor, such as HCC and cystoma; and
4. with no primary lesions found during a long-term follow-up through the regular and comprehensive examinations.[8]

2.2. Imagine and pathological examination

The primary diagnosis and discovery of lesions mainly depended on imaging examinations, including gastrointestinal endoscopy, computed tomography (CT), magnetic resonance imaging (MRI), positron emission computed tomography imaging (PET-CT, using with 18F-FDG), or octreotide scintigraphy (OctreoScan). The pathological diagnosis of HNETs was based on morphological analysis and specific neuroendocrine markers on immunohistochemistry, such as synaptophysin (Syn) and chromogranin (CgA). According to the World Health Organization (WHO) classification and the China Consensus Guideline, grading was based on the mitotic counts and/or proliferative index Ki-67. GEP-NETs could be divided into neuroendocrine tumor (NET) (G1 and G2), neuroendocrine carcinoma (NEC) (G3), and mixed adenoendocrine carcinoma (MANEC) (G3).[9] The well-differentiated G3 NETs (Ki-67 index >20%; generally less than 60%) were classified as well-differentiated NET (NET G3).[10]

2.3. Statistical analysis

All statistical analyses were performed using SPSS statistical package version 19.0 (IBM Corporation. Armonk, NY, USA). Normally distributed continuous variables were expressed as mean and standard deviation, and statistical differences between groups were assessed with the independent samples t-tests. The calculated data were compared using Chi-Squared test or Fisher exact test. Multivariate logistic regression was performed to identify independent risk factors for tumor liver metastasis. Overall survival was defined as the time from diagnosis to death or, in living patients, the time to last follow-up. Survival curves were drawn using the Graphpad Prism (version 7), and differences between subgroups were assessed with the log-rank test. Multivariate analyses using the Cox proportional hazards model were performed to identify the factors independently associated with prognosis. Statistical significance was defined if $P < .05$.

3. Results

3.1. Common clinical features in GEP-NETLM and PHNETs patients

According to the diagnostic criteria, majority HNETs were confirmed as GEP-NETLM (112 patients) while PHNETs were extremely rare and added up to 35 cases (23.8%). GEP-NETLM had a distinct male predominance (the male-to-female ratio was 2.5; $t = 29.985$ $P = .000$), while PHNETs were equal in male and female (18:17). Mean age at diagnosis was 58.0 ± 13.6 for patients with PHNETs and 59.4 ± 11.6 for patients with GEP-NETLM.

3.2. Initial symptoms

In this study, all PHNETs were identified as non-functional tumors, and pain in the upper right quadrant (40.0%, 14/35) caused by hepatic lesions compression (40.0%, 14/35) was the most common initial presentation, followed by abdominal mass (25.7%, 9/35), nausea, and vomiting (17.1%, 6/35). Concurrently, the majority of GEP-NETLM (93.7%, 105/112) had non-functional tumors (93.7%, 105/112), among which the most common symptoms were abdominal pain (29.5%, 31/105), dysphagia (13.3%, 14/105), abdominal distension (10.5%, 11/105), and emaciation (12.4%, 13/105), which were attributed to primary tumor compression. The remaining 8 cases (7.6%, 8/105) presented with liver pain due to liver occupation. Insulinoma accounted for 85.7% (6/7) of all functional tumors and has typical symptoms (hypoglycemia, palpitations), all of which are located in the pancreas. Only one case was gastrinoma, presenting with multiple refractory peptic ulcer.

3.3. Primary tumors and risk factors of liver metastasis in GEP-NET

The primary tumor sites of GEP-NETLM were summarized in Table 1. The most common primary tumor site was the stomach (39.3%), followed by the esophagus (16.9%), pancreas (19.6%) and other sites: duodenum, gallbladder, small intestine and colon (24.1%, 27/112).

Among 587 patients with GEP-NETs, the clinicopathological characteristics related to liver metastasis were listed in Table 2. Multivariate logistic regression analysis revealed that the pathological grading [odd ratio (OR): 0.283, 95% confidence interval (CI): 0.129–0.624, $P = .002$] and tumor type (OR: 0.211, 95% CI: 0.090–0.495, $P = .000$) of primary tumors were the predictors for liver metastasis.

3.4. Laboratory and imaging findings

Table 3 showed the main biochemical and serum tumor markers of the PHNETs and GEP-NETLM patients before treatment. The CEA, CA19–9 and NSE concentrations in patients with GEP-NETLM were all higher than PHNETs (all $P < .05$). A small number of HNETs patients (14.3%, 21/147) had Child-Puge scores at level B or C, while the rest were at level A. Meanwhile, there were nine HBsAg positive patients (6.1%), but no evidence of cirrhosis.

Table 1

The primary sites of GEP-NETLM among digestive system.

The primary site	Cases of digestive system (n = 587)	Cases and percentage of GEP-NETLM (n = 112)
Foregut		
Esophagus	67	19 (16.9)
Stomach	169	44 (39.3)
Duodenum	30	4 (3.6)
Pancreas	135	22 (19.6)
Gallbladder and Bile duck	26	11 (9.8)
Mid-gut		
Small intestine	10	2 (1.8)
Vermiform appendix	13	0
Ascending colon	2	1 (0.9)
Hindgut		
Transverse colon	3	0
Descending colon	3	1 (0.9)
Rectum	129	8 (7.1)

Values are n (%), GEP-NETLM = gastroenteropancreatic neuroendocrine tumors with liver metastasis, HNETs = hepatic neuroendocrine tumors.

Imaging examinations, such as US, CT, MRI, 18F-FDG PET-CT, and/or OctreoScan, were performed on 147 HNETs patients. Abdominal US was mainly manifested as hyperechoic or heterogeneous echo, with the lowest detection rate of 84.0% (21/25). Contrast-enhanced CT was the preferred examination technique, which was performed in 89.1% (131/147) of the patients, with a detection rate of >90% and showed heterogeneous enhancement of the lesions. Only 13 patients underwent contrast-enhanced MRI, in which the tumor presented an irregular mixed appearance. 18F-FDG PET-CT was often characterized by high glucose metabolism.

Combination with OctreoScan, 18F-FDG PET-CT was mainly used for the detection of extrahepatic tiny primary lesions during follow-up, and the detection rates of both were >90.0%. No evidence indicated that extrahepatic primary tumors of patients with PHNETs were found by regular and repeated imaging examinations.

3.5. Histopathologic and histomorphology characteristics

The histopathologic characteristics of all patients with PHNETs and GEP-NETLM were summarized in Table 3. Regarding the WHO tumor grading, we found that GEP-NETLM had a higher Ki-67 proliferative index (59.4 ± 2.9) than PHNETs (43.8 ± 6.1), and was more frequently classified as NEC G3 (45.7% vs 60.7%, $P = .004$). The positive rate of CgA in patients with PHNETs was significantly higher than that of GEP-NETLM ($P = .010$).

In terms of morphological features of HNETs, our data showed that PHNETs and GEP-NETLM were significantly different in tumor size ($P = .046$), site ($P = .000$) and number ($P = .000$). The mean diameter of liver lesions in PHNETs patients was larger than 6.0 cm and majority patients (65.7%) had a single nodule. More than 70% of PHNETs patients had liver tumors in single liver lobe, especially the right lobe (47.1%). In patients with GEP-NETLM, the mean diameter of the lesion was 4.1 cm, and more than half of the lesions were multiple masses located in both lobes of the live.

3.6. Treatment interventions of GEP-NETLM

Different treatments were administered to the patients, as summarized in Table 4. In patients with GEP-NETLM, 26.8%

Table 2

Clinicopathologic characteristics of 587 patients with GEP-NETs related to liver metastasis.

Characteristics of primary tumors	Total	Liver metastasis	χ^2	P value
Gender			6.444	.011
Male	363	81 (22.3)		
Female	224	31 (13.8)		
Age			11.120	.001
<60	339	49 (14.5)		
≥60	248	63 (25.4)		
First visit time			1.797	.180
≤4 weeks	204	45 (22.1)		
>4 weeks	383	67 (17.5)		
Primary tumor site			19.129	.000[a]
Foregut	427	100 (23.4)		
Mid-gut	25	3 (12.0)		
Hindgut	135	9 (6.7)		
Functional status			5.448	.035
Functional	71	7 (9.9)		
Nonfunctional	516	105 (20.3)		
Unknown	317	84 (26.5)		
Diameter of primary tumor			10.076	.002
≤2 cm	144	7 (4.9)		
>2 cm	126	21 (16.7)		
Lymph node metastasis			53.104	.000
Yes	365	36 (9.9)		
No	222	76 (34.2)		
Pathological grading			62.453	.000[a]
G1	158	2 (1.3)		
G2	140	20 (14.3)		
NET G3	39	14 (35.9)		
NEC G3	250	76 (30.4)		
Tumor type			35.698	.000[a]
NET	337	36 (10.7)		
NEC	232	71 (30.6)		
MANEC	18	5 (27.8)		
Unknown	174	41 (23.6)		
CgA			0.012	.914
Positive	206	35 (17.0)		
Negative	207	36 (17.4)		
Syn			0.859	.354
Positive	560	105 (18.8)		
Negative	27	7 (25.9)		

[a] Fishers exact test.
Values are n (%), CgA = chromogranin, MANEC = mixed adenoendocrine carcinoma, NEC = neuroendocrine carcinoma, NET = neuroendocrine tumor, Syn = synaptophysin.

(30/112) underwent surgical resection of the primary site, which was associated with a comparable favorable survival versus patients non-resected ($P = .044$) (Fig. 1B).

Only 16 GEP-NETLM patients underwent hepatectomy, and the median OS was prolonged from 16 months to 9 months compared with the patients non-resected, while the 3-year survival rate was reversed ($P = .572$). Patients with a solitary large diameter tumor (4 cases, tumor size: 5.1–8.9 cm) confined to a single liver lobe (5 cases) were more likely to undergo hepatectomy. We found no survival advantage in primary tumor resection combined with hepatectomy ($P = .588$). As the additional methods of local therapy, radiofrequency thermal ablation (RFA) and transarterial embolization (TAE)/trans-arterial chemoembolization (TACE) were performed in only 17 patients with multifocal involvement, which in combination with systemic therapy resulted in a median survival of up to 23.0 months.

Table 3

Serology, histopathologic and histomorphology characteristics of the PHNETs and GEP-NETLM.

Characteristics of hepatic tumors	PHNETs	GEP-NETLM	P value
Child-Puge score			.748[a]
Level A (5–6 scores)	32 (91.4)	94 (84.0)	
Level B (7–9 scores)	3 (8.6)	16 (14.3)	
Level C (≥10 scores)	0	2 (1.8)	
Serum tumor markers			
AFP (> 10 ng/ml)	1 (2.9)	7 (6.3)	.680[a]
CEA (>5 ng/ml)	1 (2.9)	33 (29.5)	.000[a]
CA19–9 (>37 U/ml)	2 (5.7)	26 (24.8)	.014[a]
NSE (>25 ng/ml)	1 (2.9)	32 (37.2)	.000[a]
HBsAg (Positive)	2 (5.7)	7 (6.3)	.908[a]
Pathological grading			.016[a]
G1	5 (14.3)	3 (2.7)	
G2	10 (28.6)	18 (16.1)	
NET G3	4 (11.4)	23 (20.5)	
NEC G3	16 (45.7)	68 (60.7)	
Tumor type			.220[a]
NET	19 (54.3)	44 (39.3)	
NEC	16 (45.7)	63 (56.3)	
MANEC	0	5 (4.5)	
Ki-67 PI Mean±SD (%)	43.8±6.1	59.4±2.9	.037
Unknown	0	41	
CgA			.010
Positive	25 (71.4)	32 (45.1)	
Negative	10 (28.6)	39 (54.9)	
Unknown	0	2	
Syn			.839[a]
Positive	34 (97.1)	108 (96.4)	
Negative	1 (2.9)	4 (3.6)	
Tumor number			.000
Solitary	23 (65.7)	25 (22.7)	
Multiple (≥2)	12 (34.3)	85 (77.3)	
Unknown	14	58	
Diameter of tumor			.046[a]
≤3 cm	5 (23.8)	26 (48.1)	
>3 cm	16 (76.2)	28 (51.9)	
Unknown	1	3	
Tumor location			.000
Left lobe	9 (26.5)	6 (5.5)	
Right lobe	16 (47.1)	29 (26.6)	
Double lobes	9 (26.5)	74 (67.9)	
Lymph node metastasis			.245
Yes	20 (57.1)	76 (67.9)	
No	15 (42.9)	36 (32.1)	
Unknown	5	2	
Tumor growth pattern			.202
Expansive growth	20 (66.7)	59 (53.6)	
Infiltrative growth	10 (33.3)	51 (46.4)	

Values are n (%), AFP = alpha fetoprotein, CA19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, CgA = chromogranin, GEP-NETLM = gastroenteropancreatic neuroendocrine tumors with liver metastasis, HBsAg = hepatitis B virus surface antigen (the HBsAg among 9 patients were positive but the evidence of liver cirrhosis was not observed), MANEC = mixed adenoendocrine carcinoma, NEC = neuroendocrine carcinoma, NET = neuroendocrine tumor, NSE = neuron-specific enolase, PHNETs = primary hepatic neuroendocrine tumors, PI = proliferative index, SD = standard deviation, Syn = synaptophysin.
[a] Fisher's exact test.

The majority of GEP-NETLM patients (51.8%, 58/112) received only systematic treatments, including cytotoxic chemotherapy (n=49), somatostatin analogues (n=2) and combination therapy (n=7). Among them, etoposide combined with platinum (n=38) was the most commonly used chemotherapy regimen, with no significant improvement in prognosis (3-year OS: 18.7% vs 16.0%, P=.480). Patients receiving systemic therapy alone showed a poorer prognosis than those receiving combined hepatectomy or liver-directed therapy (P=.023) (Fig. 1C).

3.7. Treatment interventions of PHNETs

Nearly half (42.9%) of PHNETs patients underwent only local treatment, including hepatectomy (n=9), RFA (n=1), TAE/TACE (n=4) and the combination therapy (n=1), with a better prognosis than systemic treatment (median OS: 29.0 months vs 15.0 months) (P=.049). Similarly, the overall survival rate of patients with hepatectomy was significantly higher than that of patients without liver tumor removed (P=.016) (Fig. 1D).

3.8. Survival analysis and related prognosis factors

Thirty five patients with PHNETs were followed up for 12 to 75 months, with a 100% follow-up rate. The 2-, 3-, and 5-years OS of PHNETs were 45.9%, 37.1%, 37.1%, respectively, significantly superior to the 35.4%, 19.3%, and 9.7% of GEP-NETLM (Fig. 1A). Multivariate analysis indicated that histological grade (P=.014), tumor type (P=.000) and treatment protocol (P=.001) were independent prognostic factors for survival (Table 5).

4. Discussion

HNETs are particular types of NETs with a potentially malignant behavior, that mostly metastasize from the digestive system, such as pancreas, stomach and gallbladder. Although the information on PHNETs etiology and pathogenesis is less available, these tumors are extremely rare and it has been hypothesized that the hepatic neuroendocrine cells may originate from intrahepatic bile duct epithelial cells, heterotopic pancreatic cells, or the adrenal tissue.[11,12] Prior reports indicated that the clinical diagnosis of PHNETs can be issued after one year of follow-up to exclude the tiny extrahepatic primary lesions and obtain the definite pathological evidence.[11,13] This study will help in establishing a database of clinical-pathological features, treatments, and prognosis of PHNETs and GEP-NETLM, thus providing evidence for early differential diagnosis, disease prognostication and patient management.

Inconsistent with other studies, we found that the incidence of PHNETs was equal in men and women, while GEP-NETLM had a distinct male predominance.[5,11] However, both groups were more common among middle-aged. Up to 80% of NETs, occurring in the liver, were metastatic lesions from other organs, especially the digestive system [14]. Studies from the United States and Korea,[15,16] confirmed that the pancreas was the most common primary tumor site, accounting for approximatively 35.0% of all GEP-NETs. In this study, we found that the major primary tumor site is the stomach (39.3%), followed by the pancreas (19.6%) and the esophagus (16.9%). In contrast to the high incidence rate of small intestine in the United States (26.8%), this rate was relatively low (1.8%) in this study, and corresponded to the result that was reported by Shin et al (3.0%).[15,16] This results inconsistency may be related to regional, ethnic, diet, and sample-size differences. As the most important predictor of liver metastasis in GEP-NETs, the degree of proliferation can be determined by the Ki-67 index and should be monitored at the initial stage.

Table 4

Treatments used for patients with PHNETs and GEP-NETLMs.

Treatment	PHNETs			GEP-NETLM		
	n	Median OS (month)	3 year OS (%)	n	Median OS (month)	3 year OS (%)
Primary tumor						
Surgical resection				30	19	15.5
No surgical resection				82	8	13.2
Hepatic tumor						
Surgical resection	13	29	48.8	16	16	9.5
No surgical resection	22	15	30.6	96	9	14.3
Local treatment	15	29	49.5	10	16	12.5
Hepatic surgical resection	9	29	50.0	6	16	20.0
Radiofrequency thermal ablation (RFA)	1	17	0	1	9	0
Transarteria embolization (TAE)/transarteria chemoembolization (TACE)	4	–	75.0	1	–	–
HR+RF or HR+TA or RF + TA	1	17	0	2	17	0
Systematic treatment	12	15	35.7	58	11	17.5
Cytotoxic chemotherapy	7	17	38.1	49	10	20.5
Somatostatin analogs	2	12	50.0	2	-	-
CC+SA	3	15	0	7	19	22.2
Combined treatment	4	25	50.0	23	22	26.8
HR+ systematic treatment	3	-	66.7	10	19	30.0
Liver-directed + systematic treatment	1	25	0	13	23	25.7
Observation	4	12	0	21	3	20.5

Values are n, CC = cytotoxic chemotherapy, GEP-NETLM = gastroenteropancreatic neuroendocrine tumors with liver metastasis, HR = hepatic surgical resection, OS = overall survival, PHNETs = primary hepatic neuroendocrine tumors, RF = RFA, SA = somatostatin analogs, TA = TAE/TACE.
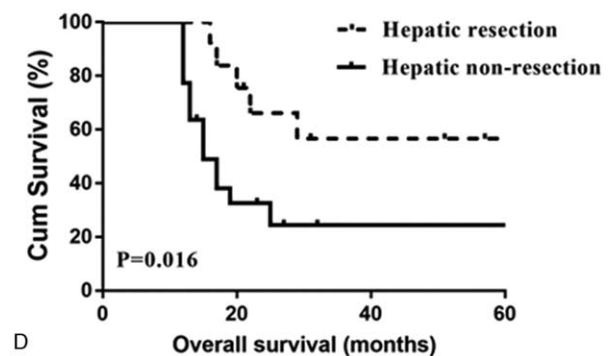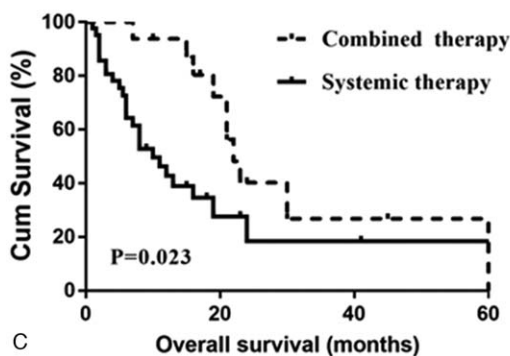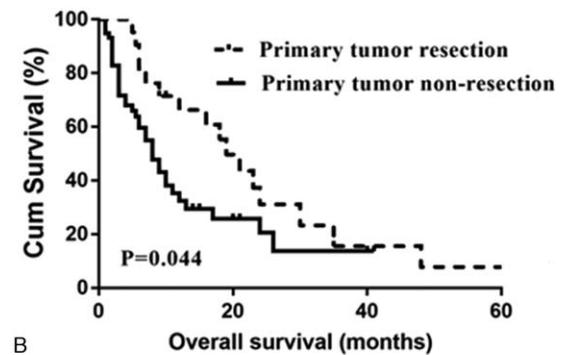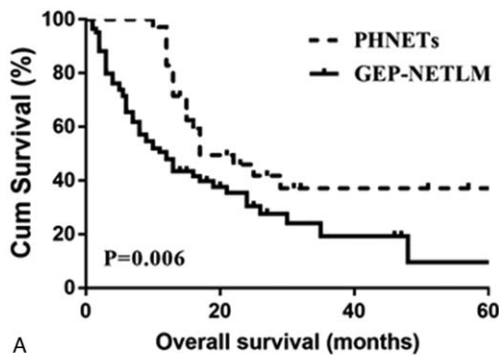

Figure 1. Kaplan–Meier analysis of overall survival. The survival curve shows that the total survival rate of the PHNETs group is higher than that of GEP-NETLM group ($P < .05$). B The survival curve shows that the total survival rate of the patients with GEP-NETLM undergo primary tumor resection group is higher than that of non-resection group ($P < .05$). C The survival curve shows that the total survival rate of the patients with GEP-NETLM undergo combined therapy group is higher than that of systemic therapy group ($P < .05$). D The survival curve shows that the total survival rate of the patients with PHNETs undergo hepatic tumor resection group is higher than that of non-resection group ($P < .05$).

Table 5

Univariate and Multivariate Analysis of the relevant Prognostic Factors associated with OS in Patients with HNETs.

Characteristics	Median OS (month)	Univariable		Multivariable	
		HR (95%CI)	P value	HR (95%CI)	P value
Group (PHNETs/GEP-NETLM)	17.0/12.0	2.012 (1.200–3.374)	.008		
Gender (male/female)	12.0/17.0	0.878 (0.553–1.394)	.582		
Age (>60/≤60)	13.0/22.0	1.530 (0.942–2.485)	.086		
Histological grade (G1/G2/NET G3/NEC G3)	-/48.0/24.0/11.0	1.486 (1.129–1.956)	.005	1.616 (1.101–2.372)	.014
Tumor type (NET/NEC/MANEC)	35.0/11.0/8.0	2.957 (1.970–4.437)	.000	2.974 (1.949–4.537)	.000
CgA (positive/negative)	22.0/15.0	1.353 (0.769–2.380)	.294		
Syn (positive/negative)	15.0/11.0	1.539 (0.620–3.823)	.353		
Size (≤3 cm/>3 cm)	12.0/16.0	0.702 (0.385–1.279)	.248		
Number (solitary/multiple (≥2))	17.0/13.0	1.589 (0.983–2.568)	.059		
Location (left lobe/right lobe/double lobes)	16.0/15.0/13.0	1.128 (0.795–1.602)	.500		
Lymph node metastasis (yes/no)	13.0/26.0	1.737 (1.053–2.866)	.031		
Tumor growth pattern (expansive/Infiltrative)	24.0/8.0	3.182 (1.920–5.276)	.000		
Treatment (local/systematic/combined/observation)	29.0/13.0/19.0/4.0	1.464 (1.148–1.865)	.002	1.606 (1.226–2.103)	.001

95% CI = 95% confidence interval, CgA = chromogranin, GEP-NETLM = gastroenteropancreatic neuroendocrine tumors with liver metastasis, HR = hazard ratio, MANEC = mixed adenoendocrine carcinoma, NEC = neuroendocrine carcinoma, NET = neuroendocrine tumor, OS = overall survival, PHNETs = primary hepatic neuroendocrine tumors, Syn = synaptophysin.

In reports conducted by Quartey and Soga et al,[17,18] PHNETs and GEP-NETs were associated with a low incidence of symptoms that were related to hormonal secretion (6.8%, 16.2%), and which may be caused by a hormone inactivation or a tumor functional deficit. PHNETs usually presented with liver pain that was attributed to the compression of hepatic lesions, while GEP-NETLM was mostly manifested as gastrointestinal symptoms. As previously reported by other studies, we found that hepatic dysfunction was less likely present in HNETs (14.3%) and that no evidence showed a related liver disease background (hepatitis and/or cirrhosis).[5,11,19] Meanwhile, according to our results, AFP, CEA, CA19-9, and NSE showed poor positive rates and had no specific diagnostic values, consistent with the reports of Qiu et al.[5,20] Non-specific clinical features of HNETs may have led to delays in decision-making for the diagnosis and treatment.

Although similar to imaging, comprehensive and careful examinations, and long-term follow-ups, could help in detecting potential extrahepatic primary lesions to distinguish primary lesions from metastatic HNETs. Although it can result in unsatisfactory specificity and sensitivity, CT/MRI is the most frequently applied radiological technique.[7,11,21] Likewise, the PET-CT clinical value is limited in well-differentiated NETs due to the insensitivity of the tracer 18F-FDG.[11,22] Compared with other detection techniques, OctreoScan is more effective in detecting the carcinoma localization and in predicting its therapeutic response.[7,23] Finding the GEP-NENLM tiny primary lesion plays a particularly crucial role in the prognostic evaluation and in considering if an early primary tumor is resected to prolong survival.

While it is ineffective to identify PHNETs and GEP-NETLM only based on the pathological morphology, pathology still remains the gold standard for HNETs diagnosis.[24] The view that HNETs have a high malignant potential, and regardless of the primary site, has been supported by the results of our research that showed that the highest incidence of HNETs was associated with NEC G3 patients. Our study proved that GEP-NETLM with a higher level of Ki-67 has a paramount importance in disease prognostication. CgA and Syn are generally considered as highly sensitive immunohistochemical markers for the diagnosis of HNETs.[10,25] The positive rate of Syn was higher than that of CgA, while the reason for the relatively high positive rate of CgA

in PHNETs is unknown compared with that of GEP-NETLM.[26] Though pathology results appeared to have limited value for differential diagnosis, morphological features of the liver tumors showed a certain significance. Our study suggested that PHNETs usually manifested as a single nodule and with a large diameter located in single liver lobe, while multiple small nodules that were located in both lobes of liver, were more common in GEP-NETLM. According to our results, the right liver lobe was the site where most HNETs occurred, which may be attributed to its larger volume and richer blood supply.[27]

HNETs treatment challenging due to their relatively indolent behavior; thus, clinicians must balance the risks and benefits of primary treatment therapies through the analysis of patient performance status and comorbidities, tumor staging, and assessment of prognostic factors.[1,28] As the only potentially curative therapy, surgical resection remains a mainstay therapy for HNETs.[29] Babak et al [30] concluded that a primary tumor resection could remove the source of liver metastasis and reduce essential hormones or growth factors that stimulate tumor proliferation, which benefit the survival of patients with GEP-NETLM. This study also supports our conclusions. Nevertheless, the high rate of high-grade or poorly differentiated tumors that are eventually resected, results in a moderate increase of 2.3%.

As demonstrated by Glazer et al,[31] the removal or destruction of focal hepatic metastases is considered as an appropriate early and aggressive therapy. For patients with PHNETs undergoing hepatectomy, the 3 year OS was significantly lower at 48.8% compared with the 78.8% (5 years OS) that was reported in the study by Knox et al.[32] In our study, this discrepancy may be explained by the high rate of poorly-differentiated NEC and intrahepatic metastasis of PHNETs. Among the patients with GEP-NETLM, the best hope for long-term survival is associated with complete surgical excision of all known primary and metastatic tumors.[33] Although inconsistent with some previous studies, our current study provides data regarding GEP-NETLM patients who benefited from a combination of hepatectomy and primary tumor surgery and who had a slightly higher 3 year OS due to the high rate of Ki-67 index that was >20% related to worse survival.[34]

Fairweather et al reported that, as alternative liver-directed therapies, RAF and TAE/TACE can be utilized as primary treatments, or as a multimodality approach for patients who are

not deemed to be candidates for surgery or have a multifocal disease, to provide symptomatic relief to the liver tumor compression and hormone secretion.[1,28] Fiore et al reported that the mean survival of 30 patients with HNETs' metastasis and who underwent TAE, was 60 months.[35] Furthermore, 90% of patients who received TACE showed significant relief of symptoms, which was confirmed by Yao KA et al.[36] In contrast to the GEP-NETLM patients, who underwent ablation or chemoembolization only, the combination of this latter with systemic therapy showed relatively favorable prognosis.

Besides, Massironi et al[37] reported that some non-liver-directed treatment strategies, such as octreotide injection and systematic chemotherapy, have also achieved a certain effect on NETs invasion. In our cohort, more than half of patients with poorly differentiated or rapidly progressive GEP-NETLM, underwent systematic therapy alone as their primary treatment option, of which platinum-based chemotherapy was the most commonly used and that showed limited efficacy on survival. Although evidence was lacking, Shen et al[38] reported outcomes for 233 patients with advanced GEP-NETs who underwent octreotide injection and demonstrated a median survival of 35.22 months. By contrast, our study confirmed that systemic therapy combined with hepatectomy or liver-directed treatment, tended to have a slightly favorable prognosis compared to any other single treatment.

Based on these data, the 5 year OS of PHNETs (37.1%) was significantly higher than that of GEP-NETLM patients (9.7%), however, both OS were lower than those reported by Shinkawa et al.[39] In our study, the histological grade was confirmed to be a significant prognosis factor, which was consistent with prior reports, which suggested a potential association between survival discrepancy and the level of Ki-67 proliferation index that is related to aggressive behavior. Meanwhile, treatment selection was reported as a vital factor in decreasing mortality. Unsurprisingly, we found that GEP-NETLM was associated with poorer outcomes compared with PHNETs; thus, early diagnosis of HNETs and the selection of appropriate treatment strategies are very important in improving patients prognosis.

The limitations of this study were as follows: First, as a retrospective analysis that was conducted by a single institution, the study has a selection bias and partial data absence. Second, the small number of patients who underwent certain treatments prevented the comparison and evaluation of the effects of treatment modalities on the prognosis. Meanwhile, irregular reviews after surgery prevented from the accurate calculation of the survival rate. Finally, serum CgA, urine 5-HIAA and the imaging examination of 68Ga-DOTATATE PET/CT, were not measured in our series; therefore, we were unable to assess these effects on the diagnosis.

5. Conclusion

As the particular types of NETs, HNETs are mainly GEP-NETLM, which seriously affect the prognosis of patients, PHNETs could not be considered until comprehensive examinations and long-term follow-ups were performed to detect the tiny extrahepatic primary lesions. PHNETs and GEP-NETLM morphological features are different and it is impossible to distinguish between them through pathology and imaging alone. Patients with PHNETs have significantly better survival than GEP-NETLM and the choice of treatment strategies shows a great significance in the prognostic evaluation.

References

[1] Fairweather M, Swanson R, Wang J, et al. Management of neuroendocrine tumor liver metastases: long-term outcomes and prognostic factors from a large prospective database. Ann Surg Oncol 2017;24:2319–25.
[2] Akerström G, Hellman P. Surgical aspects of neuroendocrine tumours. Eur J Cancer 2009;45:237–50.
[3] Rindi G, D'Adda T, Froio E, et al. Prognostic factors in gastrointestinal endocrine tumors. Endocr Pathol 2007;18:145–9.
[4] Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003;97:934–59.
[5] Qiu MJ, Chen YB, Bi NR, et al. Comparative clinical analysis of gastroenteropancreatic neuroendocrine carcinomas with liver metastasis and primary hepatic neuroendocrine carcinomas. Dis Markers 2018;2018:9191639.
[6] Nomura Y, Nakashima O, Akiba J, et al. Clinicopathological features of neoplasms with neuroendocrine differentiation occurring in the liver. J Clin Pathol 2017;70:563–70.
[7] Yang K, Cheng YS, Yang JJ, et al. Primary hepatic neuroendocrine tumors: multi-modal imaging features with pathological correlations. Cancer Imaging 2017;17:20.
[8] Lv Y, Huang C, Xu H, 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;9:479–87.
[9] Rindi G, Klimstra DS, Abedi-Ardekani B, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol 2018;31:1770–86.
[10] Chinese Pathologic Consensus Group for Gastrointestinal Pancreatic Neuroendocrine NChinese pathologic consensus for standard diagnosis of gastrointestinal and pancreatic neuroendocrine neoplasm. Zhonghua Bing Li Xue Za Zhi 2011;40:257–62.
[11] Shi C, Zhao Q, Dai B, et al. Primary hepatic neuroendocrine neoplasm: Long-time surgical outcome and prognosis. Medicine (Baltimore) 2018;97:e11764.
[12] Gurung A, Yoshida EM, Scudamore CH, et al. Primary hepatic neuroendocrine tumour requiring live donor liver transplantation: case report and concise review. Ann Hepatol 2012;11:715–20.
[13] Donadon M, Torzilli G, Palmisano A, et al. Liver resection for primary hepatic neuroendocrine tumours: report of three cases and review of the literature. Eur J Surg Oncol 2006;32:325–8.
[14] Li W, Zhuang BW, Wang Z, et al. Case report of contrast-enhanced ultrasound features of primary hepatic neuroendocrine tumor: a care-compliant article. Medicine (Baltimore) 2016;95:e3450.
[15] Wang SC, Parekh JR, Zuraek MB, et al. Identification of unknown primary tumors in patients with neuroendocrine liver metastases. Arch Surg 2010;145:276–80.
[16] Shin Y, Ha SY, Hyeon J, et al. Gastroenteropancreatic neuroendocrine tumors with liver metastases in Korea: a clinicopathological analysis of 72 cases in a single institute. Cancer Res Treat 2015;47:738–46.
[17] Quartey B. Primary hepatic neuroendocrine tumor: what do we know now? World J Oncol 2011;2:209–16.
[18] Soga J. Early-stage carcinoids of the gastrointestinal tract: an analysis of 1914 reported cases. Cancer 2005;103:1587–95.

[19] Iwao M, Nakamuta M, Enjoji M, et al. Primary hepatic carcinoid carcinoma: case report and review of 53 cases. Med Sci Monit 2001;7: 746–50.

[20] Huang YQ, Xu F, Yang JM, et al. Primary hepatic neuroendocrine carcinoma: clinical analysis of 11 cases. Hepatobiliary Pancreat Dis Int 2010;9:44–8.

[21] Li JK, Wang M, Yuan J, et al. CT and MRI findings of primary hepatic neuroendocrine neoplasm. Chin J Onclo 2017;39:600–6.

[22] Seemann MD, Meisetschlaeger G, Gaa J, et al. Assessment of the extent of metastases of gastrointestinal carcinoid tumors using wholebody PET, CT, MRI, PET/CT and PET/MRI. Eur J Med Res 2006;11:58–65.

[23] Kwekkeboom DJ, Krenning EP. Somatostatin receptor imaging. Semin Nucl Med 2002;32:84–91.

[24] Yao JC, Hassan M, Dagohoy C, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26: 3063–72.

[25] Perren A, Couvelard A, Scoazec JY, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: pathology: diagnosis and prognostic stratification. Neuroendocrinology 2017;105: 196–200.

[26] Janson ET, Sorbye H, Welin S, et al. Nordic guidelines 2014 for diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms. Acta Oncol 2014;53:1284–97.

[27] Wang LM, An SL, Wu JX. Diagnosis and therapy of primary hepatic neuroendocrine carcinoma: clinical analysis of 10 cases. Asian Pac J Cancer Prev 2014;15:2541–6.

[28] Nigri G, Petrucciani N, Debs T, et al. Treatment options for PNET liver metastases: a systematic review. World J Surg Oncol 2018;16:142.

[29] Sarmiento JM, Heywood G, Rubin J, et al. Surgical treatment of neuroendocrine metastases to the liver. J Am College Surg 2003;197: 29–37.

[30] Givi B, Pommier SJ, Thompson AK, et al. Operative resection of primary carcinoid neoplasms in patients with liver metastases yields significantly better survival. Surgery 2006;140:891–8.

[31] Glazer ES, Tseng JF, Al-Refaie W, et al. Long-term survival after surgical management of neuroendocrine hepatic metastases. HPB (Oxford) 2010;12:427–33.

[32] Knox CD, Abderson CD, Lamps LW, et al. Long-term survival after resection for primary hepatic carcinoid tumor. Ann Surg Oncol 2003;10:1171–5.

[33] Sham JG, Ejaz A, Gage MM, et al. The impact of extent of liver resection among patients with neuroendocrine liver metastasis: an international multi-institutional study. J Gastrointest Surg 2019;23:484–91.

[34] Schreckenbach T, Hübert H, Koch C, et al. Surgical resection of neuroendocrine tumor liver metastases as part of multimodal treatment strategies: a propensity score matching analysis. Eur J Surg Oncol 2019;45:808–15.

[35] Fiore F, Del Prete M, Franco R, et al. Transarterial embolization (TAE) is equally effective and slightly safer than transarterial chemoembolization (TACE) to manage liver metastases in neuroendocrine tumors. Endocrine 2014;47:177–82.

[36] Yao KA, Talamonti MS, Nemcek A, et al. Indications and results of liver resection and hepatic chemoembolization for metastatic gastrointestinal neuroendocrine tumors. Surgery 2001;130:677–82.

[37] Massironi S, Conte D, Sciola V, et al. Contrast-enhanced ultrasonography in evaluating hepatic metastases from neuroendocrine tumours. Dig Liver Dis 2010;42:635–41.

[38] Shen C, Shih YCT, Xu Y, et al. Octreotide LAR among elderly patients with neuroendocrine tumors: a survival analysis of SEER-medicare data. Cancer Epidemiol Biomarkers Prev 2015;24:1656–65.

[39] Shinkawa H, Takatsuka S, Kaizaki R, et al. Postoperative outcomes of primary hepatic neuroendocrine carcinomas: review article. Osaka City Med J 2013;59:105–13.