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Original Article

Prognostic factors of patients with gastroenteropancreatic neuroendocrine neoplasms

Pao-Yuan Huang [a], Kai-Lung Tsai [b], Chih-Ming Liang [a], Wei-Chen Tai [a], Kun-Ming Rau [c], Keng-Liang Wu [a], Chao-Cheng Huang [d], Seng-Kee Chuah [a,*]

[a] *Division of Hepato-Gastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan*
[b] *Division of Colon and Rectal Surgery, Department of Surgery, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan*
[c] *Division of Hematology-Oncology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan*
[d] *Department of Pathology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan*

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KEYWORDS
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Abstract There is an increasing trend in the incidence of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) worldwide. The aim of the present study was to identify the prognostic factors of patients with GEP-NENs. A cross-sectional, retrospective chart review study was conducted among patients with pathologically proven GEP-NENs between January 2003 and December 2016 at Kaohsiung Chung-Gung Memorial Hospital. A total of 97 patients who met the inclusion criteria were included (male/female = 56/41, age: 57.7 ± 15.4 years). The presentation, clinical characteristics, and disease outcomes were reviewed and analyzed. The most common primary site of the GEP-NENs was the rectum (49.5%), followed by the pancreas (17.5%), duodenum (11.3%), stomach (10.3%), colon (6.2%), and appendix (5.2%), and most GEP-NENs were hormonally nonfunctional (94.8%). There were 56 tumors classified as G1 neuroendocrine tumors (NETs), 9 as G2 NETs, and 14 as G3 neuroendocrine carcinoma (NEC). Metastasis was found in 15 patients (15%). Curative treatments, such as surgery or endoscopic resection, were performed in 83.5% of patients (n = 81). The mean overall survival duration was 107.2 ± 7.8 months. The estimated 3- and 5-year overall survival rates for all patients were 84% and 82%, respectively. Logistic regression analysis showed that large tumor size, non-rectal NENs, high histopathological grading, lymphatic metastases and distant

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* Corresponding author. Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, 123 Ta-Pei Road, Niao-Song District, Kaohsiung 833, Taiwan.
E-mail address: chuahsk@seed.net.tw (S.-K. Chuah).

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metastases were associated with poor survival. This study suggested that the presence of lymphatic or distant metastases at diagnosis is an independent risk factor for poor prognosis in patients with GEP-NENs.
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Introduction

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are rare tumors that originate from the neuroendocrine cells of the embryologic gut [1]. These cells are capable of secreting neuropeptides and hormones that cause distinct clinical syndromes, such as carcinoid syndrome. These tumors can involve any part of the gastrointestinal tract and the pancreas and have a wide range of malignant potential, from benign to poorly differentiated tumors [2]. Based on the Surveillance Epidemiology and End Results (SEER) Program registries in the US, there was a significant increase in the incidence of NENs from 1973 (1.09/100,000) to 2004 (5.25/100,000), but Asian/Pacific Islanders had a lower incidence of neuroendocrine tumors (NETs)(3.19 per 100,000) than White populations (4.92/100,000) [3]. Tsai et al. reported that the age-standardized incidence rate of NENs in Taiwan increased from 0.30/100,000 in 1996 to 1.51/100,000 in 2008 [4].

Because of the low incidence, tumor heterogeneity, nonspecific symptoms at presentation, lack of awareness, and nonuniform nomenclatures and classifications, GEP-NEN remains a poorly understood disease, and delayed diagnosis is common among patients with GEP-NENs [1,3]. Many studies have reported the epidemiology, pathology, clinical features, treatment, and prognostic factors of GEP-NENs mainly in the Western population. Furthermore, epidemiological data based on large registry databases may not include detailed clinical and pathological features of GEP-NENs. Therefore, the aim of this study was to identify the prognostic factors of patients with GEP-NENs.

Materials and methods

Ethics statement

The study protocol was approved by the institutional review board and the Ethics Committee of Chang Gung Memorial Hospital (IRB201601540B0). The ethics committee waived the requirement for informed consent in this study, and all the data were analyzed anonymously.

Data source

This was a cross-sectional and retrospective chart review study conducted between January 2003 and December 2016, and patients with a diagnosis of carcinoid tumor, neuroendocrine neoplasm, neuroendocrine tumor, or neuroendocrine carcinoma according to pathology reports were included in our study. Patients with tumor origins other than the stomach, small intestine, pancreas, colon, appendix were excluded.

Patient demographics and clinical characteristics, including symptoms on presentation, the date of diagnosis, the location of tumors, staging by the American Joint Committee on Cancer (AJCC) (7th edition) [5], the presence of lymphatic and/or distant metastasis, treatment modality, duration of follow-up, and outcomes, were obtained from the reviewed medical records. The tumor characteristics recorded were size, mitotic count per high-power field and the expression of Ki-67, synaptophysin and chromogranin A as detected by immunohistochemistry. The patients were classified according to tumor grading by the 2010 World Health Organization (WHO) classification [6].

Recurrence-free survival (RFS), defined as the period from tumor removal by surgical or endoscopic resection until the detection of recurrent or metastatic disease, was examined. Overall survival was defined as the time from the diagnosis to death, last contact, or Feb 28, 2017.

Statistical analysis

Descriptive analyses were used to determine differences in the baseline clinicopathological characteristics of patients. Kaplan—Meier survival curves were constructed for each variable. A Cox proportional hazard model was used for multivariate analysis of hazard ratios. All statistical analyses were conducted using the statistical software package SAS (version 9.3; SAS Institute Inc., Cary, NC, USA). A two-sided p value < 0.05 was considered statistically significant.

Results

The clinical characteristics of the study group are shown in Table 1. A total of 97 patients with pathological confirmation of GEP-NENs were included (male/female = 56/41, age: 57.7 $\pm$ 15.4 years, ranged 15—90 years). Overall, the most frequently involved primary site for GEP-NENs was the rectum (n = 48, 49.5%), followed by the pancreas (n = 17, 17.5%), duodenum (n = 11, 11.3%), stomach (n = 10, 10.3%), colon (n = 6, 6.2%), and appendix (n = 5, 5.2%).

There were 79 patients in the present study that had sufficient data for pathologic staging according to the 2010 WHO criteria. Three patients who were diagnosed before 2010 were reclassified based on information regarding the mitotic count and Ki-67 index from the pathology report according to the 2010 WHO classification. G1 was the most common pathologic stage (n = 56, 70.9%). Of the GEP-NENs, 11.4% and 17.7% were in the G2 and G3 (neuroendocrine carcinoma, NEC) stages, respectively. Regarding

Table 1 Clinical characteristics and overall survival of patients with gastroenteropancreatic-neuroendocrine neoplasms (GEP-NENs).

Factors	Number (%)	Mean (months)	95% CI	P value
All patients	97	107.18	91.86–122.49	
Gender				0.093
Male	56 (57.7%)	98.66	78.41–118.92	
Female	41 (42.3%)	102.72	93.98–122.49	
Age (years old)				0.10
<50	25 (25.8)	131.28	118.47–144.08	
>=50	72 (74.2)	91.99	79.03–104.95	
Primary tumor site				<0.01
Stomach	10 (10.3)	70.19	35.10–105.27	
Pancreas	17 (17.5)	93.71	71.36–116.07	
Duodenum	11 (11.3)	88.55	49.70–127.40	
Appendix	5 (5.2)	-*	-*	
Colon	6 (6.2)	11.42	7.30–15.53	
Rectum	48 (49.5)	122.92	105.78–140.07	
WHO classification, 2010				<0.01
NET G1	56 (70.9)	108.87	98.32–119.41	
NET G2	9 (11.4)	51.89	28.04–75.73	
NEC	14 (17.7)	19.47	8.48–30.49	
AJCC/UICC classification				<0.01
I	64 (66.0)	132.11	121.23–142.99	
II	9 (9.3)	86.96	52.51–121.41	
III	10 (10.3)	29.19	14.43–43.95	
IV	14 (14.4)	63.23	29.15–97.30	
Distant metastasis				<0.01
Negative	84 (86.6)	117.95	104.47–131.43	
Positive	13 (13.4)	60.96	26.36–95.56	
Lymphatic metastasis				<0.01
Negative	75 (77.3)	124.08	109.78–138.37	
Positive	22 (12.7)	24.36	14.09–34.63	
Hormonal activity				0.45
Non-functional	92 (94.8)	112.56	98.65–126.46	
Functional	5 (5.2)	89.80	44.68–134.92	
Initial treatment				<0.01
Curative treatment	82 (84.5)	119.17	104.43–133.90	
Palliative treatment	15 (15.5)	31.24	15.61–46.87	

tumor, node, and metastasis (TNM) staging according to the AJCC classification, patients were most commonly diagnosed with stage I tumors (n = 64; 66%) followed by stage IV tumors (n = 14; 14.4%), stage III tumors (n = 10, 10.3%), and stage II tumors (n = 9, 9.3%) at presentation. Fig. 1 shows the distributions of the different histological grades of GEP-NENs among the different tumor stages. As high as 96% of the stage I tumors were G1, and 4% of them were G2. In stage II patients, 43% was G1, 28.5% was G2, and the other 28.5% was G3, while only 22% was G1 and 11% was G2 in stage III patients. In fact, 67% of the stage III tumors were G3. In stage IV patients, 55% was G3, 36% was G2 and only 9% was G1.

Metastases were found in 27 patients (27.8%) at the time of diagnosis, including 13 patients with distant metastases and 22 with lymphatic metastases. The most common distant metastatic site was the liver (n = 10, 76.9%). The highest percentage of distant metastatic disease was noted for stomach NENs (n = 3; 30%), followed by pancreatic NENs (n = 5; 29.4%), colon NENs (n = 1; 16.7%), duodenum NENs (n = 1, 9.1%), and rectal NENs (n = 3, 6.3%). In the present study, only 7.1% of the G1 NENs were diagnosed as metastatic disease, while 55.6% of G2 NENs and 92.9% of NEC had metastases. However, all of the appendiceal NENs were diagnosed as localized disease.

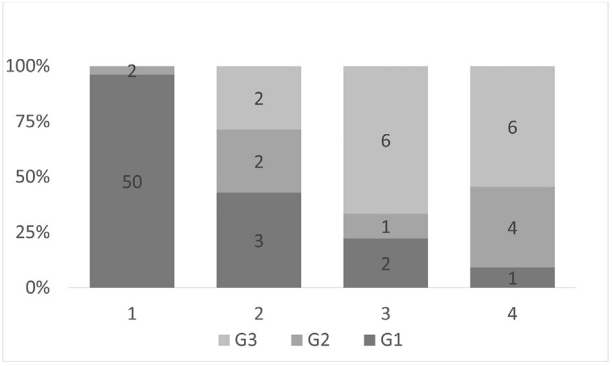

Fig. 1. The distributions of different histological grades of gastroenteropancreatic neuroendocrine neoplasms among the different stages of tumors.

Thirty-six patients (37%) were asymptomatic at diagnosis, and most of them had rectal NENs (n = 21), which were diagnosed by colonoscopy at a health check-up or during follow-up after treatment for colorectal polyps. Nonfunctional tumors were common among GEP-NENs (n = 92, 94.8%), and there were only 5 functional tumors in the present study (5.2%) (Table 1). Among these 5 functional tumors, two were insulinomas, one was a gastrinoma, and two were NENs with carcinoid syndrome. Of the 92 nonfunctional cases, abdominal pain was the most frequently presented symptom (n = 33, 35.9%), and the other nonspecific symptoms were blood in stool (n = 20, 21.7%), bowel movement changes (n = 14, 15.2%), weight loss (n = 7, 7.6%), nausea or vomiting (n = 5, 5.4%), anal pain (n = 2, 2.2%), and jaundice (n = 3, 3.3%).

Most patients underwent initial curative endoscopic (n = 20, 20.6%) or surgical resection (n = 61, 62.9%), but 5 patients (5.2%) received palliative surgery to relieve tumor-related intestinal or biliary obstructions. Chemotherapy was administered in 9 patients with metastasis at diagnosis, mostly as adjuvant chemotherapy after curative surgery. The chemotherapy prescribed was folinic acid and oxaliplatin with 5-fluoruracil (FOLFOX) for 3 patients and platinum-etoposide for the other 6 patients. Two patients with bone metastases received palliative radiotherapy. Local-regional transarterial embolization (TAE) was performed in 4 patients with liver metastases. Noncurative treatment with somatostatin analogs was used on 5 patients with unresectable pancreatic NETs with distant metastases or functional NETs (3 with pancreatic NENs, 1 with stomach NENs, and 1 with duodenal NENs). Two patients received supportive care for symptom relief due to other comorbidities.

The details of the overall survival of patients with GEP-NENs are summarized in Table 1. The median follow-up duration was 34.8 months (1—138 months). During the observation period, 14 patients died. The mean overall survival duration was 107.2 ± 7.8 months. The estimated 3- and 5-year overall survival rates for all patients in the present study were 84% and 82%, respectively (Fig. 2). Among the 27 patients with metastases, twelve died (44.4%), while only two of the 70 patients without metastases (2.9%) died during the observation period.

As demonstrated in Table 2, univariate analysis showed that G2 or G3 tumors, tumors larger than 1 cm, high tumor stage, lymphatic or distant metastasis on presentation, and initial palliative treatment were significant predictors of poor outcome (Supplementary Figs. 1—5). In standardized multivariate models, lymphatic and distant metastases were independent risk factors for poor prognosis.

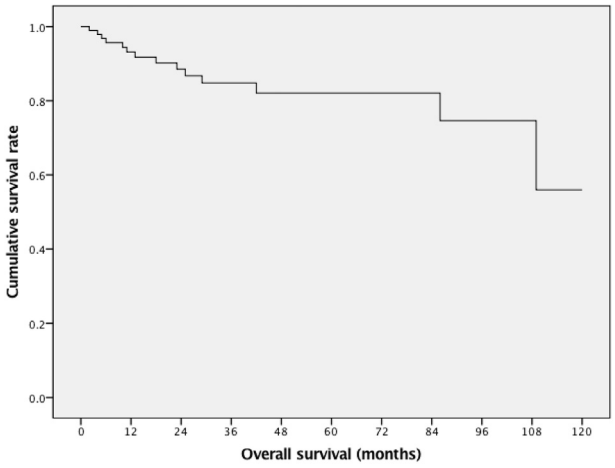

Fig. 2. Survival curve for patients with gastroenteropancreatic neuroendocrine neoplasms.

Discussion

Most epidemiological data on GEP-NENs are from the United States or European countries; thus, there is a paucity of data describing the epidemiology and prognostic factors of GEP-NENs among Asians in Asia. This study was conducted to identify prognostic factors for patients with GEP-NENs and found that lymphatic and distant metastases were independent risk factors for poor outcomes.

The average age at GEP-NEN diagnosis in the present study was 57.7 ± 15.4 years, which is comparable to that in other studies. Most of the sites with neuroendocrine tumors were in the gastrointestinal system. A large-scale analysis of NENs (n = 35,618) using the SEER registry data revealed that the most common primary tumor site of GEP-NENs in White patients is the small intestine, while the rectum is the most common site in Asian/Pacific Islanders [3]. The distribution of the primary tumor site in our study was similar to that in other Asian population studies, such as those in China, with a high percentage of rectal NENs (Table 3) [4,7]. This disparity in organ distribution suggests that race may affect the development of GEP-NENs, but there is no scientific evidence to support this hypothesis. In Taiwan, because of the health exam policies and the easy availability of endoscopy, rectal tumors are found in their early stages much more easily, while other tumors require further examination that is not routinely performed, which might influence tumor incidence.

The present study showed that most GEP-NENs are nonfunctional tumors. Carcinoid syndrome, Zollinger-Ellison syndrome, Whipple triad, Verner-Morrison syndrome, glucagonoma syndrome, and somatostatinoma syndrome are typical symptoms of functional NENs [8,9]. Only 5.2% of GEP-NENs in our study were functional tumors, and 80% of them were pancreatic NENs. The mean age at the diagnosis of functional tumors (42 years old) was almost 17 years younger than that of nonfunctional tumors because these symptomatic patients usually seek medical assistance due to the presence of significant and specific symptoms caused by excess hormones. Carcinoid syndrome accounted for 40% of functional tumors, and all of these tumors were associated with liver metastasis. Carcinoid syndrome is common among disseminated diseases, especially liver metastasis. The liver inactivates secretory products released into portal circulation, while GEP-NETs with liver metastasis release tumor products into systemic circulation [10,11].

G1 NENs were the most common type of GEP-NENs in our study, which is consistent with other studies. However, G2 NENs and NEC accounted for more than half of the tumors in the colon and stomach. Overall, NEC constituted less than 20% of all cases. Nearly 90% of well-differentiated GEP-NENs were diagnosed at stage I according to the AJCC

Table 2 Univariate and multivariate analysis of risk factors for survival of patients with GEP-NENs.

Variables		Univariate			Multivariate		
		Relative risk of death	95% confidence interval	P value	Relative risk of death	95% confidence interval	P value
Gender	Male	1					
	Female	0.35	0.10—1.26	0.11			
Age	<50	1					
	>=50	4.71	0.62—36.02	0.14			
Primary site	Rectum	1					
	Non-rectum	3.94	1.09—14.20	0.04	—		0.06
Functionality	Non-functional	1					
	Functional	1.79	0.39—8.25	0.46			
Symptom on presentation	Incidental finding	1					
	Symptomatic disease	3.74	0.83—16.77	0.09	—		0.53
Size	0—1 cm	1					
	>1 cm	7.54	1.67—34.06	<0.01	—		0.16
Metastasis[a]	Negative	1					
	Positive	27.91	6.15—126.71	<0.01			
Lymphatic metastasis	Negative	1					
	Positive	86.25	10.80—688.60	<0.01	52.72	5.69—488.70	<0.01
Distant metastasis	Negative	1					
	Positive	7.39	2.50—21.82	<0.01	7.02	1.66—29.65	<0.01
Histopathological grading	G2 vs. G1	9.22	129—65.86	0.03	—		0.14
	G3 vs. G1	29.59	5.71—153.37	<0.01	—		0.08

[a] Metastases included distant and lymphatic metastasis.

classification. However, as high as 43.5% of G2 NENs and NEC were diagnosed at stage IV, which is a severe disease stage in these two disease categories. Surprisingly, distant metastases at diagnosis were observed in only 13.4% of all patients in our study, which was lower than the rates identified in other reports (23%—34%) [12,13].

Up to 37% of the GEP-NEN patients were asymptomatic and therefore diagnosed accidentally, which explained the early stage of the diseases in these patients. Most of the diagnoses were colonic NENs, which were diagnosed by colonoscopy at a health check-up or during follow-up after treatment for colorectal disease. Tsai et al. reported that the incidence of NENs in Taiwan has increased steadily from 1996 to 2001 and has increased at a more accelerated pace since 2002. The fastest increase in the incidence of GEP-NENs was noted in the rectum [4]. The possible reasons for this increase may include increased surveillance for colorectal cancer by endoscopy, increased awareness of NENs among clinicians, and improved diagnostic technology.

Surgery is the mainstay curative treatment or cytoreductive therapy for palliative purposes. Endoscopic resection is also indicated for localized stomach or colorectal NENs with low malignant potential [16]. For patients with liver metastasis, treatment modalities include surgery, systemic medical treatment, and local-regional procedures, such as radiofrequency ablation and TAE [17—19].

Table 3 Top five most common sites of GEP-NENs in Taiwan, China, the US, and Norway.[a]

	Tsai et al. Taiwan [4]		Zhang et al. China [7]		Hauso et al. US white [14]		Boyar Cetinkaya et al. Norway [15]	
	Site	% of GEP-NENs	Site	% of GEP-NENs	Site	% of GEP-NENs	Site	% of GEP-NENs
1	Rectum	47.9	Rectum	58.9	Small intestine	35.3	Small intestine	33.0
2	Stomach	14.1	Pancreas	13.7	Rectum	24.6	Appendix	23.8
3	Pancreas	11.3	Stomach	9.5	Colon	14.7	Pancreas	15.9
4	Colon	10.1	Small intestine	8.3	Stomach	11.0	Colon	10.8
5	Small intestine	9.9	Colon	4.8	Pancreas	8.2	Rectum	9.4

Abbreviations: GEP-NENs, gastroenteropancreatic neuroendocrine neoplasms.

Systemic chemotherapy is recommended for pancreatic NENs, metastatic G2 NENs, and NEC. Combination chemotherapy with etoposide and platinum is the most common regimen prescribed for the treatment of poorly differentiated G3 NENs [19]. The reported response rate of poorly differentiated NEC to etoposide and platinum (EP) therapy ranges from 14 to 42% [20,21]. The diverse outcomes may be caused by different study populations, including non-GEP-NEC patients and hepatobiliary NEC patients.

In our study, there was no statistically significant difference in overall survival stratified by gender or age. Other studies, including the Surveillance, Epidemiology, and End Results Program, revealed poorer overall survival among men and older adults than among women and younger adults [3,4,22,23]. Nevertheless, a trend of higher relative risks of death for men and older patients than for women and younger patients (odds ratios of 2.86 and 4.71, respectively) was observed in our study. This discrepancy could be due to the small sample size in our study.

Distant metastatic disease was related to a 7-fold higher risk of death in our study. There was no disease-related mortality in patients with stage 1 NENs during the observation period. The 5-year overall survival among patients with stage 4 NENs was 51% in our study, which was consistent with that in other studies [14,24].

There are some limitations in our study. First, this study used a retrospective design at a single center, included a small sample size, and evaluated a small number of events, such as mortality; thus, the results may not be representative of the entire GEP-NEN population in Taiwan. The study also revealed heterogeneous treatments between different clinicians due to the lack of uniform guidelines for the management of GEP-NENs in Taiwan. In addition, the follow-up time in our study was short for a slow-growing disease. Moreover, our patients were mainly classified by the 2010 WHO classification rather than the more recently updated 2017 WHO classification.

In conclusion, this study suggested that the presence of lymphatic and distant metastases at diagnosis is an independent risk factor for poor prognosis in patients with GEP-NENs.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.kjms.2018.05.009.