RESEARCH ARTICLE

Clinicopathological Features and Prognosis of Gastroenteropancreatic Neuroendocrine Tumors: Analysis from a Single-institution

Yu-Jie Zeng[1&], Lu Liu[1&], Heng Wu[1], Wei Lai[1], Jie-Zhi Cao[2], He-Yang Xu[1], Jie Wang[1], Zhong-Hua Chu[1*]

Abstract

Background: The gastroenteropancreatic neuroendocrine neoplasm (GEP-NEN) is the most common type of neuroendocrine neoplasm. We summarized data in our centre to investigate the clinicopathological features, diagnostic methods, therapeutic approaches and prognosis for this neoplasm to increase knowledge of this disease in Asian populations. Method: A total of 122 patients treated at Sun Yet-san Memorial Hospital of Sun Yat-sen University between January 2000 and December 2011 were analyzed retrospectively. Results: Pancreas was the most common site of involvement (65/122, 53.3%); this disease has no special symptoms; positive rates of chromogranin A (CgA) and synaptophysin (Syn) were 81.1% and 87.7%, respectively. The positive rate of Syn had statistical difference among the three grades, but not CgA. Some 68 patients had G1 tumors, 32 G2 tumors and 22 G3 tumors, and Chi-square test showed that higher grading was correlated with worse prognosis (χ^2=32.825, *P*=0.0001). A total of 32 patients presented with distant metastasis, and 8 cases emerged during following up. Cox proportional hazards regression modeling showed that the tumor grade (*P*=0.01), lymphatic metastasis (*P*=0.025) and distant metastasis (*P*=0.031) were predictors of unfavorable prognosis. The overall 5-year survival rate was 39.6%, the 5-year survival rate of G1 was 55.7%, and the G2 and G3 were 34.2% and 0%, respectively.Conclusions: The incidence of gastroenteropancreatic neuroendocrine tumors has risen over the last 12 years. All grades of these diseases metastasize readily, and further research regarding the treatment of patients after radical surgery is needed to prolong disease-free survival.

Keywords: Gastroenteropancreatic neuroendocrine neoplasms - clinical characteristics - prognosis - treatment

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Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms composed of cells containing dense-core neuroendocrine secretory granules in their cytoplasm. These tumors are relatively rare and display a diverse spectrum of clinical presentations; approximately two-thirds of NETs are found in the gastrointestinal tract(Modlin et al., 2003; Modlin et al., 2008; Younes, 2008). According to an analysis of the National Cancer Institute's Surveillance, Epidemiology and End Results database (SEER, http://seer.cancer.gov/data/index. html), which is currently the largest epidemiologic series, the incidence of NETs has been rising substantially over the past 30 years. The main explanation for this increase is improved awareness of the disease among physicians and pathologists as well as improved diagnostic techniques.

For many years, NETs have been the subject of debate regarding the optimal nomenclature, grading, staging and classification of these tumors. Utilizing the latest 2010 World Health Organization (WHO) classification (Bosman, 2010) and the China Consensus Guidelines for the standards of histopathology diagnosis for NETs, we performed a comprehensive retrospective study to examine the relationship between clinical pathological characteristics and survival from GEP-NETs. Based on 12 years of data from our institution, we aimed to increase knowledge concerning this disease in Asian populations by summarizing and analyzing the data from our clinical center, concerning the clinicopathological features, diagnostic methods, therapeutic methods and prognosis of gastroenteropancreatic neuroendocrine tumors.

*[1]Department of Gastroenteropancreatic Surgery, The Sun Yat-sen Memorial Hospital, Sun Yat-sen University, [2]Department of Second Surgery, Baiyun District Hospital of Traditional Chinese Medicine, Guangzhou, China [&]Equal contributors *For correspondence: sumschuzhonghua@hotmail.com*

Table 1. Characteristics of Imaging Studies

Imaging studies	Site	Manifestation	Case tested	Positive tests	
				N	%
Endoscopy			57	52	91.2
Gastroscopy	Esophagus, stomach, duodenum	Ulcer type, occupying lesions	19	18	94.7
Colonoscopy	Colonrectum,appendix	Occupying lesions	35	32	91.4
Small intestinal endoscope	Jejunum/ileum	Occupying lesions, polypus	3	2	66.7
Ultrasound	Pancreas, liver	Hypoechoic masses, occupying solid lesions	112	103	91.9
EUS	Pancreas	Hypoechoic masses	39	38	97.4
CT scan	Pancreas, liver, stomach, Colon, rectum	Occupying solid lesions	103	98	95.1
MRI	Pancreas, liver	Occupying solid lesions	65	60	92.3
PET-CT	All of above	Occupying solid lesions	9	8	88.9

EUS, endoscopic ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission computed tomography imaging

Materials and Methods

A retrospective analysis was conducted of 122 patients from Sun Yet-san Memorial Hospital of Sun Yat-sen University between January 2000 and December 2011. The histology of each patient was reviewed according to WHO classification and the China Consensus Guidelines. In addition, clinical information from our institution was assembled including the age, gender, locations, clinical symptoms, endoscopic and radiographic features, histopathological characteristics, metastasis patterns, treatment modalities and outcomes.

The pathological diagnosis of the NETs in this series depended on typical morphological findings and the expression of neuroendocrine markers, including chromogranin A and/or synaptophysin (Erickson et al., 2004). We used two specific antibodies to stain the tumors in our studies and confirm the diagnosis. The antibodies of chromogranin A and synaptophysin were provided by the company of Millipore (United State) and cell signal technology (United State), respectively. The 2010 WHO NET classification system was applied to all of the GEP-NETs, using slides stained with hematoxylin and eosin and immunohistochemistry (MIB1 monoclonal antibodies against the Ki-67 antigen). The cell proliferation index used the Ki-67 index, which is based the following levels, ≤2%, 3–20%, and >20% per 500–2000 tumor cells in the most active regions or hot spots. The mitotic rate was used at levels of <2, 2–20, and >20 mitoses per 10 high-power fields in the most active regions or hot spots. These areas were restained and recounted to estimate the tumor proliferative activities. According to the Ki-67 index, the grading of G1, G2 and G3 was less than or equal to 2%, 3–20% and greater than 20%, respectively. Likewise, tumors with mitotic rates of less than two under 10 HPF were classified as G1; those with rates from 2 to 20 in 10 HPF were classified as G2, and those with rates greater than 20 in 10 HPF were classified as G3. If the grading of the Ki-67 index disagreed with the mitotic rate, the higher of the two was given priority.

Overall survival was defined as the time from diagnosis to death or the time to last follow-up in living patients. Survival rate was estimated according to the Kaplan–Meier method and the Cox proportional hazards regression model. Differences between subgroups were assessed by the log-rank test, and $P < 0.05$ was statistically significant. SPSS 13.0 software was used for the statistical analyses.

Results

Clinical Characteristics

Among the 122 Chinese patients with GEP-NENs, 55 (45.1%) were men and 67 (54.9%) were women. The mean age was 49.13 ±16.21 years. The most common tumor sites were the pancreas (53.3%, 65/122), followed by the rectum (22.9%, 28/122), stomach (13.1%, 16/122) and appendix (4.1%, 5/122). Lesions of the duodenum and ileum occurred at the same rate (2.5%, 3/122), and the site with the lowest occurrence was the colon (1.6%, 2/122). Non-functional tumors comprised the majority of the GEP-NENs (61.5%, 75/122).

The most common initial presentation was abdominal pain (77.9%, 95/122), which was not specific for the diagnosis of this tumor. Other non-specific clinical symptoms or sighs were abdominal distension (46.7%, 57/122), gastrointestinal bleeding or melena (34.4%, 42/122), dizziness and disturbance of consciousness (19.7%, 24/122), change in bowel habits (19.7%, 24/122), hyperspasmia (11.5%, 14/122), abdominal mass without symptom (8.2%, 10/122), and jaundice without pain (3.3%, 4/122). Insulinoma comprised 91.5% (43/47) of the functional tumors; the other functional tumor was gastrinoma (8.5%, 4/47). Typical clinical manifestations included hypoglycemia, dizziness and disturbance of consciousness and peptic ulcer, which heralded functional NENs. Otherwise, carcinoid syndrome did not present in our study.

Imaging studies

The most frequently used examination procedures included endoscopy, ultrasound, endoscopic ultrasonography (EUS), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission computed tomography imaging (PET-CT used with 16 F-FDG). However, we did not have access to somatostatin receptor scintigraphy in our institution to locate tumors. The results of these examinations are summarized in Table 1. The tumors usually appeared as solid lesions under endoscopy or on CT scan. Ultrasound and EUS usually presented the tumors as hypo-echoic masses. The

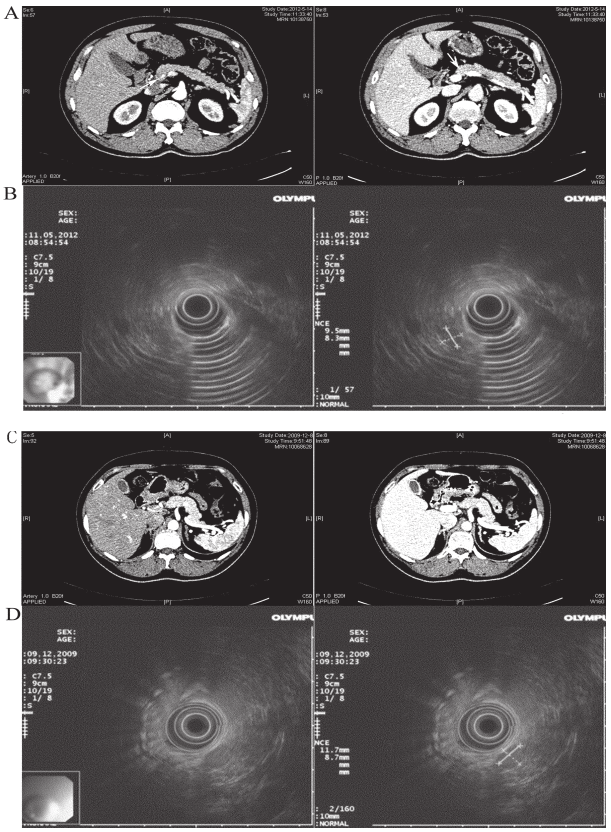

Figure 1. The imaging studies between CT scan and EUS (A and B) CT scan and EUS can both detect the tumor in the pancreas. (C and D) the EUS detect the tumor in the pancreas, but CT scan not

small diameter pancreatic neoplasms were more easily diagnosed with endoscopic ultrasonography (97.4%, 38/39) (Figure 1).

Pathologic characteristics

The features of the pathological morphology of GEP-NETs under light microscopy were as follows: 1) The morphology of the cells of the neuroendocrine tumor (NET), including G1 and G2, was consistent and displayed a uniform distribution with a rich cytoplasm. The cancer tissue arranged itself in a certain shape, such as a gland bubble, a small tubular structure, a cable, or a solid mixed form. The level of differentiation was highly visible. The shapes of the nuclei were regular, and their sizes were uniform. However, nuclear division was rare. 2) The characteristics of the neuroendocrine carcinomas (NEC) included large cell NEC and small cell NEC. These cancer cells had different shapes and sizes, and a moderate amount of cytoplasm. Nuclear division was readily observed. The cancer cells were arranged in nests or block-like pieces, and their boundaries were not clear. Differentiation was present to a moderate degree. 3) The mixed adenoneuroendocrine carcinomas (MANEC) consisted of both adenocarcinoma and neuroendocrine carcinoma cells, and the proportion of each was need more than 30 percent (Figure2 and 3).

Based on the post-operation data, the mean diameter of the tumors was 3.91 cm (0.6–20 cm). Furthermore, 12.7% (14/110) of the tumors were smaller than or equal to 1 cm in diameter, 62.7% (69/110) ranged in size from 1 to 5 cm,

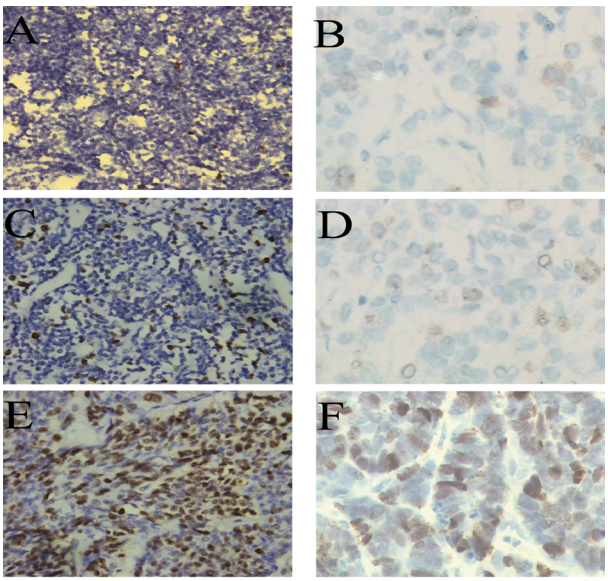

Figure 2. The morphological characteristic and expression of Ki-67 under light microscope. (A and B) show the morphological characteristic of G1, and the expression of ki-67 is less than or equal to 2%. (C and D) show the morphological characteristic of G2, and the expression of ki-67 is range from 3% to 20%. (E and F) show the morphological characteristic of G3, and the expression of ki-67 is more than 20%. (Left photos for 100X (Right photos for 400X)

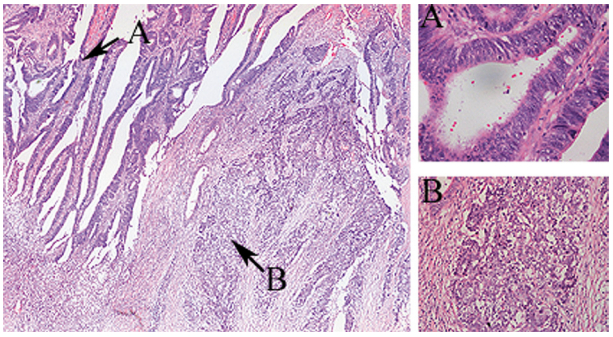

Figure 3. Mixed adenoneuroendocrine carcinoma (MANEC). We can see the composition of adenocarcinomas at the top left and the composition of neuroendocrine tumor at the bottom right

and 24.6% (27/110) of the tumors were larger than 5 cm. Immunohistochemical staining showed an 81.1% positive rate of CgA and an 87.7% positive rate of Syn. The Ki-67 index and mitotic rate were assessed in all of the patients to estimate their proliferative activities. Over half (55.7% 68/122) of the tumors were G1, 26.2 %(32/122) were G2, and 18.1%(22/122) were G3. The most common tumor type was NET (81.9%), followed by NEC (15.6%) and MANEC (2.5%). Lymphatic metastasis had occurred in 42.7% (47/110) of the patients. Distant metastasis was a frequent event at diagnosis with an occurrence of 19.7% (24/122); the incidence increased to 26.2% (32/122) during follow up. The liver was one of most frequently involved organs: liver metastasis occurred in 29 (90.7%) of 32 patients during the course of the disease. Among the 29 patients with liver metastasis, 22 presented with synchronous liver metastasis, whereas the other seven presented with metachronous liver metastasis during

Table 2. Overall Survivals

Factor	Overall survival					
	Number	Mean (Months)	Std. Error	95%CI	X^2	*P*
All patients	122	50.4	5.8	39.1~61.7		
Sex					0.946	0.331
Male	55	38.1	8.0	22.4~53.8		
Female	67	60.9	7.7	45.8~76.0		
Age					0.029	0.866
<50	54	53.2	7.6	38.3~68.2		
>50	68	45.5	8.7	28.3~62.6		
Site					0.084	0.771
Gastrointestinal tract	57	40.4	6.3	28.1~52.7		
Pancreas	65	53.5	7.8	38.1~68.8		
Tumor grading					32.825	0.0001
G1	68	66.4	7.7	51.3~81.4		
G2	32	35.3	8.2	19.3~51.3		
G3	22	9.8	1.6	6.6~12.9		
Diameter of tumor					1.422	0.491
<=1cm	14	35.4	7.1	21.4~49.4		
>1,<=5cm	69	51.0	8.0	35.3~66.8		
>5cm	27	36.3	7,.5	21.7~50.9		
Tumor type					26.323	0.0001
NET	100	58.7	6.4	46.1~71.2		
NEC	19	9.8	1.9	5.9~13.6		
MANEC	3	10.0	2.0	6.1~13.9		
Functional status					0.945	0.331
Functionan	47	60.6	8.6	43.6~77.5		
Nonfunctional	75	33.9	4.6	24.9~42.9		
Lymphatic metastasis					11.577	0.001
Positive	47	24.8	6.5	12.0~37.5		
Negative	75	68.7	7.0	55.0~82.3		
Distant matastasis					10.387	0.001
Yes	32	23.0	4.9	13.4~32.7		
No	90	62.9	7.0	49.2~76.8		

Table 3. Cox Proportional Hazards Regression Model

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Sex	0.077	0.360	0.046	1	0.830	1.081	0.533	2.189
Age	-0.130	0.311	0.174	1	0.677	0.878	0.477	1.617
Grade	0.896	0.348	6.625	1	0.010	2.450	1.238	4.846
Site	0.664	0.349	3.609	1	0.057	1.942	0.979	3.850
Diameter	-0.371	0.193	3.702	1	0.054	0.690	0.473	1.007
Type	-0.173	0.514	0.113	1	0.737	0.841	0.307	2.304
Lymphatic metastasis	-0.813	0.364	5.006	1	0.025	0.443	0.217	0.904
Distant metastasis	-0.806	0.374	4.639	1	0.031	0.447	0.214	0.930

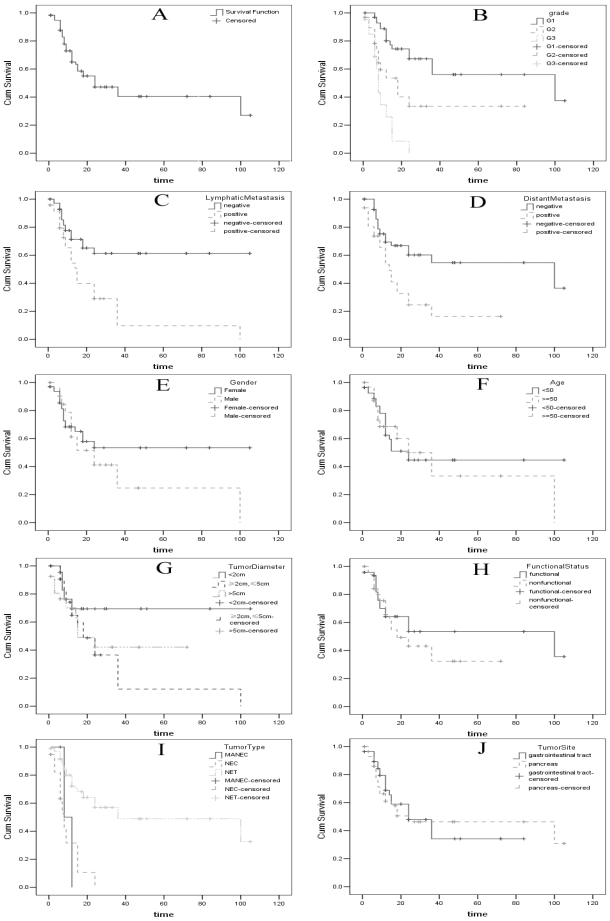

Figure 4. Overall survivals (A) Overall survival in all patients. (B) Overall survival by histological grading. (C) Overall survival by condition of lymphatic metastasis. (D) Overall survival by condition of distant metastasis. (E) Overall survival by sex. (F) Overall survival by age at diagnosis. (G) Overall survival by tumor diameters. (H) Overall survival by functional status. (I) Overall survival by tumor type. (J) Overall survival by site of tumors

follow-up. Other locations involved were the lung (6.2%, 2/60) and the cavitas pelvis (3.1%, 1/32).

Therapeutic interventions

A large percentage of the patients underwent surgery (90.2%, 110/122). The purpose was curative intent in 78.2% (86/110) of the cases and palliative care in 21.8% (24/110) of the patients. Local-regional therapies such as transcatheter hepatic arterial chemoembolization (TACE), radiofrequency or other ablative techniques were performed in only 10 cases (8.2% of the population). Chemotherapy was administered in 30 patients; the chemotherapy regimens included oxaliplatin-capecitabine or 5-FU (16 patients, 53.3%), platinum-etoposide (6 patients, 20%), oxaliplatin-TS-1 (2 patients, 6.7%), Gemzar alone or in combination with oxaliplatin (2 patients, 6.7%) and irinotecan-5-FU (2 patients, 6.7%). Our data did not show the use of the somatostatin analogue Octreotide. Six cases (4.9%, 6/122) with progressive malignant disease were treated only with supportive care.

Survival and prognostic factors

Follow up was long term in 102 out of the 122 patients; the median survival time for these patients was 50.4±5.8 months (95% CI, 39.1~61.7). The 1-, 3- and 5-year survival rates were 64.7%, 48.2% and 39.6%, respectively. The major causes of death were tumor-related complications (84.3%), and treatment-related adverse events (11.8%) and other diseases (3.9%). An analysis was performed on the sex, age, primary tumor site, histopathological grading, tumor diameter, tumor type, functional tumors, lymphatic and distant metastasis to identify the prognostic factors associated with survival. Univariate analysis confirmed that patients at the G1 phase without lymphatic or distant metastasis and classified as NET had higher survival rates than other types of NENs. However, age, sex, tumor diameter, primary tumor site and

Table 4. The Overall Survival and the Positive Rates for Specific Immunity Indicators

Specific immunity	Overall survival						Comparison for the positive rates			
indicators	Number	Mean (Months)	Std. Error	95%CI	X^2	*P*- value*	G1	G2	G3	*P*- value*
CgA					0.411	0.522				
Positive	99	49.6	6.3	37.3~61.9			51	30	18	0.071
Negative	23	48.4	10.3	28.2~68.5			17	2	4	
Syn					0.049	0.825				
Positive	107	50.6	6.1	38.5~62.7			55	31	21	0.041
Negative	15	45.3	11.4	22.9~67.6			13	1	1	
NSE					0.816	0.366				
Positive	70	52.1	8.2	36.1~68.1			37	19	14	0.702
Negative	52	46.6	8.2	30.5~62.6			31	13	8	

*The statistical method is chi-square test and the *p*-value is Fisher Exact Test

tumor functional status showed little impact on the overall survival rate. The statistics for survival time and other data are provided in Table 2. The survival curves are shown in Figures 4. According to the Cox proportional hazards regression model, which removed the confounding factors, the tumor grade and the rates of lymphatic and distant metastasis had an impact on the overall survival rate (Table 3).

Discussion

Our data show that the incidence of GEP-NENs has risen over the last 12 years, as has been reported in previous studies (Konishi et al., 2007; Yao et al., 2008; Ploeckinger et al., 2009; Garcia-Carbonero et al., 2010; Estrozi et al., 2011; Lim et al., 2011). In this study, we investigated the pathologic features of GEP-NENs using the latest histopathologic diagnosis consensus and analyzed overall survival by Univariate analysis and Cox proportional hazards regression modeling. We utilized our clinical data to evaluate the epidemiology, clinical pathological features, treatment and prognosis of GEP-NET among a population in China.

Although GEP-NENs were widely distributed in most organs, the pancreas is the principal site (53.3%) of GEP-NENs. The rectum was the most frequent site within the gastrointestinal tract, followed by the stomach and appendix. However, the jejunum/ileum accounted for no more than 3% of tumors, and the colon was the least frequent tumor site in our study. A similar distribution of NENs was also found in other two Asian populations (Lim et al., 2011; Wang et al., 2012), but tumor distribution is different in the non-Asian Races. The rectum and jejunum/ileum were the most common sites for NENs in the SEER Program tumor registry from the United States in North America, and pancreatic NENs were only the third most common site for NENs (Yao et al., 2008). In contrast, in the Spanish database, the National Cancer Registry for Gastroenteropancreatic Neuroendocrine Tumors (RGETNE) (Garcia-Carbonero et al., 2010), the pancreas and jejunum/ileum were the most frequent tumor locations. Moreover, the small intestine was the most frequent site of origin, followed by the colon and rectum, in the NRC-Norwegian Registry of Cancer (Hauso et al., 2008). These latter two registries are both from Europe. Brazilian registries (Estrozi et al., 2011), from South America, have reported that the stomach was the most frequency tumor site. Second were the small intestine and rectum. However, the pancreas was the fourth most frequent site. To sum up, it is clearly that the primary site of neuroendocrine tumors differs between races.

NENs can be classified into functional and non-functional tumors according to the presence or absence of symptoms associated with hormone overproduction (Klimstra et al., 2010). In this study, the most common initial presentation was abdominal pain, which is not a specific symptom. Several patients suffered from hypoglycemia or dizziness. These symptoms even disturbed consciousness and the lesions were commonly misdiagnosed initially until arriving at a diagnosis of insulinoma. Insulinoma comprised the largest number of functional NENs in our study. Therefore, improved vigilance is necessary when these symptoms are observed.

The choice of imaging technique depends on the characteristics of the particular type of NET and its presentation. Ultrasound was the most common inspectional method in our study; this is because of its convenience and non-invasive nature, but it is less sensitive than other methods. CT can achieve a higher rate of diagnosis. However, endoscopic ultrasonography (EUS) provided the highest positive identification rate (97.4%) in this study. The introduction of EUS provides unique advantages in evaluating the upper gastrointestinal tract and pancreatic system (Krstic et al., 2005; Patel et al., 2008; Starkov et al., 2010), especially for tumors less than 1.0 cm in diameter and micrometastases. There were 14 patients with tumor diameters less than 1.0 cm in our study. All of these tumors were diagnosed using EUS; five of these tumors were missed by CT. Somatostatin receptor scintigraphy is considered a comprehensive imaging modality for many neuroendocrine tumors, but unfortunately, our institution has not had this methodology for the past decade.

An imaging examination is the first step toward disease diagnosis. However, the final definite diagnosis depends on the pathological analysis of biopsy or surgical specimens, including cell morphology (as discussed above) and immunohistochemical staining. The European Neuroendocrine Tumor Society (ENETS) and the North American Neuroendocrine Tumor Society (NANETS) have published standards for diagnosis and pathology

reports of NENs in 2009 and 2010 (Kloppel et al., 2009; Klimstra et al., 2010), respectively. Furthermore, the WHO revised the nomenclature and classification of GEP-NENs in 2010 (version 4). In 2011, China established its own classification system for NENs. All of the cases in our study were analyzed anew, using the latest standards, to offer a precise diagnosis. The two immunohistochemical staining markers, CgA and Syn, are an indispensable test for diagnosis, and at least one of these two tests must be positive. Neuron Specific Enolase (NSE) is another marker of NENs, but its specificity is lower than CgA and Syn. In our study, the rates for positive results for CgA, Syn and NSE were 81.1%, 87.7% and 57.4%, respectively. However, the positive rates for these three specific indicators do not have a bearing on prognosis. Moreover, we can conclude that the positive rates of CgA and NSE were not significantly different among the three grades. However, there was a statistically significant difference among the three grades for Syn (Table 4). Furthermore, our comparison between each of the two grades found that the only the difference between G1 and G2 was statistically significant; this was not the case for the other two comparisons. Nonetheless, there is a contradiction between the P value and the 95%CI, which may be due to the limited sample size. Thus, a larger sample size is needed for a more precise conclusion regarding the positive rates of the three immunohistochemical staining markers among the three grades.

Among the many therapeutic options for NENs, surgery is the treatment of choice (Plockinger et al., 2004; Modlin et al., 2006; Oberg et al., 2009; Yalcin, 2011). A variety of operations is available to reduce the tumor load and improve survival, and the extent of surgical resection depends on the tumor size and origin. If possible, removal of the primary tumor by a palliative operation can reduce the secretion of bioactive substances and render medical treatment more effective. Transcatheter hepatic arterial chemoembolization (TACE), radiofrequency or other ablative techniques were usually adopted to treat metastasis to the liver. Chemotherapy, primarily adjuvant or therapeutic chemotherapy was used for patients with or without radical surgery. According to published studies, several chemotherapeutic regimens, most of which are either platinum based or fluorouracil based, are suggested. However, a definitive guideline is still unavailable (Mitry et al., 1999; Fjallskog et al., 2001; Kouvaraki et al., 2004; Sun et al., 2005; Hainsworth et al., 2006). In our study, all regimens utilized were either the platinum based or fluorouracil based, but the number of cases for cytotoxic chemotherapy was too small to obtain a statistically significant conclusion. There are no reports examining whether GEP-NENs benefit from adjuvant chemotherapy after radical surgery. Eight cases of distant metastasis emerged in the follow up to radical surgery, two of them did not receive any treatment after the surgery, and the remainder underwent cytotoxic chemotherapy. The effect was limited because of the restricted sample sizes. At present, several clinical trials examining these treatments have been completed and several are ongoing. A substantial benefit from the use of Lanreotide or Octreotide LAR combined with a targeted drug, such as everolimus or sunitinib, has been indicated (Faiss et al., 1999; Oberg et al., 2004; Kulke et al., 2008; Yao et al., 2008; Rinke et al., 2009; Yao et al., 2010; Raymond et al., 2011; Yao et al., 2011). These trials are mainly targeting disease progression. Currently, the optimal treatment for patients who have undergone radical surgery is still unclear. Discovering treatments to improve disease-free survival after radical surgery is an important area for future study.

According to our Cox proportional hazards regression modeling, the tumor grade, lymphatic metastasis and distant metastasis are the main factors impacting prognosis. Of these, the tumor grade, according to the Ki-67 index and mitotic rate, was most important for prognosis. Previous studies have shown that higher grading is correlated with worse prognoses. Our study shows results similar to those of earlier studies (G1 vs. G2: χ^2 =9.164, P=0.002; G1 vs. G3: χ^2=36.627, P<0.0001; and G2 vs. G3: χ^2=5.065 P=0.024, α=0.05). The 5-year survival rates for grades G1, G2, and G3 in our series are 55.7%, 34.2% and 0%, respectively. Nevertheless, we found that the differences in the distant metastasis rates among the grades were not statistically significant (The metastasis rates of the grades were G1: 12/68, G2: 12/32, and G3: 8/22; χ^2=5.857, P=0.053 > α=0.05). From these results, we conclude that all grades of this disease have the same probability for metastasis and that follow-up therapy after surgery is indeed important for all three grades.

In conclusion, GEP-NENs are diseases with no specific symptoms. Therefore, early diagnosis of these diseases is difficult, and a combination of imaging and tissue immunohistochemical methods should be used. Multidisciplinary therapy for these diseases is also important. All grades of these diseases metastasize readily, and further research regarding the treatment of patients after radical surgery is needed to prolong disease-free survival.

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