

RESEARCH ARTICLE

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# Relationship between clinical characteristics and survival of gastroenteropancreatic neuroendocrine neoplasms: A single-institution analysis (1995–2012) in South China

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## Abstract

**Background:** Gastroenteropancreatic neuroendocrine neoplasm (GEP-NEN) is the most common type of neuroendocrine tumors accounting for 65–75% of neuroendocrine neoplasms (NENs). Given the fact that there are few studies on GEP-NENs among Chinese patients, we performed a retrospective study in South China.

**Methods:** Totally 178 patients with GEP-NENs treated at the First Affiliated Hospital of Sun Yat-sen University between January 1995 and May 2012 were analyzed retrospectively.

**Results:** Pancreas was found the most common site of involvement (34.8%). 149 patients (83.7%) presented as non-functional tumors with non-specific symptoms such as abdominal pain (33.7%); carcinoid syndrome was not found in this study. Several methods are useful for localization of GEP-NENs, yielding varied detection rates from 77.8% to 98.7%. Positive rates of chromogranin A (CgA) and synaptophysin (Syn) immunohistochemically were 69.1% and 90.2%, respectively. 87 patients (51.5%) had G1 tumors, 31(18.3%) G2 tumors and 51 (30.2%) G3 tumors. Neuroendocrine tumor (NET), neuroendocrine carcinoma (NEC) and mixed adenoendocrine carcinoma (MANEC) were 69.8%, 27.2% and 3.0%, respectively. 28.1% of patients presented with distant disease. Surgery was performed in 152 (85.4%) patients, and overall 5-year survival rate was 54.5%. Functionality, G1 grading and NET classification were associated with favorable prognosis in univariate analysis. Distant metastasis contributed to unfavorable prognosis of these tumors.

**Conclusions:** Nonfunctional tumors with non-specific symptoms account for the majority of GEP-NENs. Diagnosis depends on pathological classification. Multidisciplinary treatments could help improve the outcome.

**Keywords:** Gastroenteropancreatic neuroendocrine neoplasms, Clinical pathological characteristics, Survival

## Background

Neuroendocrine neoplasms, which originate from neuroendocrine cells distributed throughout the body, comprise a heterogeneous family with a wide and complex clinical behaviors [1]. The incidence of NENs ranges from 2.5 to 5 cases per 100,000 in the United States, and the gastrointestinal tract is the most commonly affected site [2,3]. 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 the largest epidemiologic series nowadays, the incidence of NENs has been rising substantially in the past 30 years.

NENs have been the subject of debate regarding optimal nomenclature, grading, staging and classification of these tumors for many years. A uniform World Health Organization (WHO) classification greatly facilitates the comparison of clinical, pathological and prognostic features and results of treatment in GEP-NENs, and so do the China Consensus Guidelines for the standards of histopathologic diagnosis as well [4,5].

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The incidence of NENs, the treatments and survival of Caucasians have been well studied in western countries such as United States, Norway, Spain, German and the United Kingdom [2,3,6-9]. But for Asian population [10-13], especially for Chinese population, available information on these cancers is rather limited [14]. Therefore, it requires detailed data for comprehensive knowledge of NENs in China. Based on the 17-year data of our hospital, a comprehensive retrospective study was performed to examine the relationship between clinical pathological characteristic and survival of GEP-NENs. To our knowledge, it is the first study providing information on these tumors using the latest histopathologic diagnosis consensus from an Asian country.

## Methods

178 patients with histologically confirmed sporadic GEP-NENs from The First Affiliated Hospital, Sun Yat-sen University (1995–2012) were enrolled in this study to collect clinical information including age, gender, locations, clinical syndromes, endoscopic and radiographic features, histopathological characteristics, metastasis patterns, treatment modalities and outcomes.

The histology of each patient was reviewed according to the WHO classification [4] and China Consensus Guidelines [5]: First, immunohistochemical staining of CgA and Syn, which are all neuroendocrine markers, were performed to recognize the histological patterns of these tumors. Specific peptide hormones (eg. insulin, glucagon and somatostatin) staining methods were not regularly used only when a functional neuroendocrine neoplasm was considered. Second, the Ki-67 index ( $\leq 2\%$ , 3–20%, and  $>20\%$  per 500–2000 tumor cells in the most active regions or hot spots, respectively) or mitotic rate (1, 2–20, and  $>20$  mitoses per 10 high-power field in the most active regions or hot spots, respectively), which was re-stained or recounted, was used to estimate the tumor proliferative activities. Tumors with a Ki-67 index of  $<2\%$  were classified as G1 tumors, index of 3–20% were classified as G2, greater than 20% as G3. Likewise, tumors with mitotic rates of  $<2/10$  HPF were classified as G1, those of 2 to 20/10 HPF were classified as G2, greater than 20/10 HPF as G3. Once the grading of Ki-67 index disaccorded with the mitotic rate, the higher one was preferred. Thus, GEP-NENs were classified as NET (G1 and G2), NEC (G3) and MANEC (G3).

Overall survival was defined as the time from diagnosis to death or last follow-up in living patients. Survival rate was estimated according to the Kaplan–Meier product limit method, and differences between subgroups were assessed by the log-rank test with  $P < 0.05$  as statistically significant. SPSS 16.0 was used for statistical analysis.

The study was approved by the ethics committee of The First Affiliated Hospital Sun Yat-sen University (with

a reference number: [2012]317) and complied with the Declaration of Helsinki.

## Results

### Clinical features

Among the 178 Chinese patients with GEP-NENs, 108 (60.7%) were men and 70 (39.3%) were women; male-to-female ratio was 1.54. The mean age was  $50.96 \pm 15.01$  years. The most common sites were the pancreas (62/178, 34.8%), followed by rectum (36/178, 20.2%), stomach (25/178, 14.0%), duodenum (13/178, 7.3%), metastatic NENs of unknown primary (12/178, 6.7%) and esophagus (7/178, 3.9%). Other sites included appendix, jejunum/ileum, Vater's ampulla at 12.9% (23/178). Non-functional tumors comprised the majority of GEP-NENs (149/178, 83.7%), whereas functional tumors accounted for the other 16.3%. A variety of gastrointestinal manifestations were caused by the effect of local compression on nearby tissues in nonfunctional tumors. The most common initial presentation was abdominal pain (60/178, 33.7%), which was not specific for the diagnosis of tumor. Other non-specific symptoms were gastrointestinal bleeding (29/178, 16.3%), jaundice (16/178, 9.0%), progressive dysphagia (9/178, 5.1%), diarrhea (8/178, 4.5%), abdominal distension (6/178, 3.4%) and so on. Incidental diagnosis occurred in 10.1% of cases which were usually asymptomatic. Insulinoma comprised 93.1% of functional tumors, which mainly occurred in pancreas, occasionally followed by the substantially rarer glucagonoma and vasoactive intestinal peptidoma (only 1 case respectively in our study). Typical symptoms included hypoglycemia, epileptic seizure and secondary diabetes mellitus, which heralded functional NENs, but carcinoid syndrome did not present in our study. The demographics and presenting symptoms of GEP-NENs are listed in Table 1.

### Imaging studies

The most frequently used examination procedures included endoscopy, ultrasound, endoscopic ultrasonography (EUS), computed tomography (CT) scan, magnetic resonance imaging (MRI), and positron emission computed tomography imaging (PET-CT, using with  $^{18}\text{F}$ -FDG). Endoscopy provided the highest detection rate of 98.7% (74/75). EUS was performed on 37 patients, of which a lesion was found in 34 patients, promised a detection rate of 91.9%. MRI and PET-CT, was performed in only about 10% of patients, respectively. Tumors usually appeared as polypoid prominences, ulcer type or cauliflower-like neoplasm under endoscopy; whereas on CT scan, they appeared as local space-occupying lesions which were significantly enhanced by iodinated contrast. Ultrasound and EUS usually demonstrated the tumors as rounded, homogeneous, hypoechoic, well-defined and well-vascularized masses (Table 2).

**Table 1 Characteristics of study population (N = 178 patients)**

Site	All patients		Men, n(%)	Women, n(%)	Clinical symptoms	Main signs
	N	%				
Pancreas	62	34.8	32(51.6)	30(48.4)	Abdominal pain, Jaundice, Hypoglycaemia	Jaundice
Rectum	36	20.2	29(80.6)	7(19.4)	Gastrointestinal bleeding, Abdominal pain, Diarrhea	Rectum mass
Somach	25	14.0	16(64.0)	9(36.0)	Abdominal pain, Gastrointestinal bleeding, Dysphagia	Abdominal tenderness
Duodenum	13	7.3	10(76.9)	3(23.1)	Abdominal pain, Jaundice, Gastrointestinal bleeding	Jaundice
Metastasis of unknown primary	12	6.7	6(50.0)	6(50.0)	Abdominal pain, Asymptomatic, Fatigue	Hepatomegaly
Esophagus	7	3.9	5(71.4)	2(28.6)	Progressive dysphagia	No signs
Appendix	6	3.4	2(33.3)	4(66.7)	Abdominal pain, Abdominal distension	Rebound pain in the Mcburney's point
Jejunum/ileum	4	2.2	3(75.0)	1(25.0)	Gastrointestinal bleeding, Small bowel obstruction	Anemia
Gallbladder	4	2.2	1(25.0)	3(75.0)	Jaundice, Asymptomatic	Jaundice
Vater's ampulla	3	1.7	3(100)	0(0)	Jaundice, Abdominal pain,	Jaundice
Peritoneum	3	1.7	0(0)	3(100)	Abdominal pain, Asymptomatic	Abdominal mass
Cecum	1	0.6	1(100)	0(0)	Abdominal pain	Abdominal mass
Choledoch	1	0.6	1(100)	0(0)	Jaundice	Jaundice
Greater omentum	1	0.6	0(0)	1(100)	Asymptomatic	No signs

**Pathologic characteristics**

Overall, the mean diameter of tumors was 3.95 cm (0.4–25 cm): 38.6% were smaller than 2 cm in diameter, 29.7% ranging from 2 to 4 cm, and 31.7% larger than 4 cm. Immunohistochemistry staining determined a 69.1% positive rate of CgA and a 90.2% positive rate of Syn. Ki-67 index and mitotic rate were assessed in 127 and 118 specimens to estimate the proliferative activities. Over half (51.5%) of the tumors were G1, 18.3% were at G2 and 30.2% at G3. The most common tumor type was NET (69.8%), followed by NEC (27.2%) and MANEC (3.0%). Approximately half of the assessed tumors (53/100, 53.0%) originated from gastrointestinal tract and biliary system with muscularis or serosa

infiltration at diagnosis. Local infiltration and lymphatic metastasis occurred in 23.0% and 27.0% of patients respectively. Distant metastasis was a frequent event at diagnosis with an occurrence of 23.0% (41/178), which increased to 28.1% (55/178) during follow up. The liver was one of most frequently involved organs: liver metastasis occurred in 44 (80.0%) of 55 patients in the disease courses. Among the 44 patients, 29 presented with synchronous liver metastasis, whereas other 15 presented with metachronous liver metastasis during follow-up. Other locations that tumors involved were the peritoneum (12.7%, 7/55), cavitas pelvis (9.1%, 5/55), bone (7.3%, 4/55) and ovary (5.5%, 3/55). The most common site of primary tumor associated with widespread

**Table 2 Characteristics of imaging studies**

Imaging studies	Site	Manifestation	Case tested	Positive tests	
				n	%
Endoscopy	gastrointestinal tract		75	74	98.7
Gastroscope	esophagus, stomach, duodenum	ulcer type, bulge type, invasive type	34	34	100
Duodenoscope	duodenum	bulge type	3	3	100
Small intestinal endoscope	jejunum/ileum	small intestinal hemorrhage	2	1	50.0
Colonoscope	rectum, appendix	polypoid prominences, submucosal uplift, cauliflower-like neoplasm	36	36	100
Ultrasound	pancreas, liver, gallbladder, choledoch	hypoechoic masses, well delimited and vascularized	63	49	77.8
EUS	pancreas, duodenum, stomach	hypoechoic masses	37	34	91.9
CT scan	pancreas, liver, stomach	local space-occupying lesions	123	98	91.9
MRI	pancreas, duodenum, biliary	local space-occupying lesions	20	19	95.0
PET-CT	pancreas, rectum	local space-occupying lesions	20	19	95.0

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

disease at diagnosis was cecum (100.0%), followed by jejunum/ileum (75.0%), gallbladder (50.0%), duodenum (38.5%), Vater's ampulla (33.3%) and stomach (28.0%) (Table 3).

### Therapeutic interventions

85.4% patients underwent a surgery with curative intent (75.9%) or for palliative purpose (9.6%). Different types of endoscopic radical surgery were performed, including endoscopic mucosa resection (EMR), endoscopic submucosal dissection (ESD) and endoscopic electroexcision. Local-regional therapies such as transcatheter hepatic arterial chemoembolization (TACE), radiofrequency or other ablative techniques were carried out only in 11 cases (6.2% of the population). Chemotherapy and biological therapy were performed in 31 patients, among which 15 received chemo regimen, 8 received biological therapy and 8 received both. The most common first-line chemo combinations included platinum-etoposide (6 patients, 3.4%), oxaliplatin- capecitabine (2 patients, 1.3%), oxaliplatin-TS-1 (2 patients, 1.3%) and so on. Octreotide, a somatostatin analogue, was frequently administered at a dose of 20–40 mg/month as a biological therapy, combined with chemotherapy in 1 patient (0.6%) after surgery and in 7 patients (3.9%) with unresectable tumors. 14 (7.9%) cases with progressive malignant disease were treated only with supportive care.

**Table 3 Pathologic characteristics**

Characteristics	Case tested	Positive tests	
		n	%
Immunohistochemistry			
CgA	149	103	69.1
Syn	143	129	90.2
Tumor grading			
G1	169	87	51.5
G2	169	31	18.3
G3	169	51	30.2
Tumor type			
NET	169	118	69.8
NEC	169	46	27.2
MANEC	169	5	3.0
Infiltration/Metastasis			
Muscularis/Serosa infiltration	100	53	53.0
Adjacent tissue/Capsule infiltration	178	41	23.0
Lymphatic metastasis	178	48	27.0
Distant metastasis			
At initial diagnosis	178	41	23.0
During follow-up	178	55	28.1

CgA, Chromogranin A; Syn, Synaptophysin; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; MANEC, mixed adenoendocrine carcinoma.

### Survival and prognostic factors

136 out of 178 patients received long-term follow up with a median duration of 8.6 years (range 0.03–13.48 years). Median survival was not obtained during the observation period. The 1-, 3- and 5-year survival rates was 74.4%, 66.7% and 54.5% respectively, and 25 patients had died at the last follow-up (14.0%). The major causes of death were tumor-related complications (84.0%), and treatment-related adverse events (12.0%); other disease contributed the other 4.0%. An analysis was performed on patients' age, gender, primary tumor site, histopathological grading, classification and condition of metastasis to identify prognostic factors for survival. Univariate analysis confirmed that functional tumors, patients were at G1 phase and classified as NET were superior to other types of NENs in survival. Distant metastasis also contributed to the prognosis of these neuroendocrine tumors. However, age, sex, primary tumor site had little impact on overall survival. The mean survival time and statistic data were provided in Table 4. Survival curves were displayed in Figure 1.

### Discussion

The WHO classification system of gastroenteropancreatic neuroendocrine tumors was adopted in previous studies [3,7,8,10-12,14]. Some of these studies only focused on particular types of GEP-NENs such as well-differentiated endocrine tumors, poorly differentiated endocrine carcinomas or a single site of tumors (pancreas, colon or rectum). Our study investigated the pathologic features of GEP-NENs by using the latest histopathologic diagnosis consensus for the first time. It also analyzed any possible tumor site of digestive system including pancreas, biliary and peritoneal cavity. This study should contribute to establishing a database of the epidemiology, clinical pathological features, treatment and prognosis of GEP-NENs in China.

It is confirmed in our study that GEP-NENs comprise a heterogeneous group in relation to their primary locations. Previous researches indicated that the small intestine and appendix were the most predominant NENs locations [2,15-17]. But according to our study, pancreas is the principal site of GEP-NENs. The rectum is the most frequent sites of gastrointestinal tract, followed by the stomach and duodenum, whereas the jejunum/ileum accounts for no more than 2% tumor cases. A similar distribution of NENs was also found from a Korean study [10], which observed that rectum was the most common primary site of tumor in 470 available cases, followed by the pancreas, stomach and duodenum. Results from another three registries including SEER, National Cancer Registry for Gastroenteropancreatic Neuroendocrine Tumors (RGETNE, <http://www.retegep.net>) and Norwegian Registry of Cancer (NRC)

**Table 4 Overall survival**

Factors	Overall survival				χ <sup>2</sup>	P
	Number	Mean (years)	95% CI			
All patients	136	9.5	8.1-11.0			
Sex				2.053	0.152	
Female	54	9.9	8.5-11.3			
Male	82	8.7	6.7-10.6			
Age				0.259	0.611	
≤50	60	9.9	8.0-11.8			
>50	76	7.8	5.9-9.6			
Site				2.385	0.123	
Gastrointestinal tract	77	6.7	5.4-8.0			
Pancreas	46	11.1	9.3-12.9			
Functional status				6.691	0.006	
Functional	22	NR	NC			
Nonfunctional	114	7.7	6.1-9.2			
Tumor grading				9.087	0.011	
G1	63	10.8	8.7-12.9			
G2	25	3.5	2.6-4.3			
G3	41	4.1	2.8-5.4			
Tumor type				6.634	0.010	
NET	88	10.1	8.1-12.1			
NEC + MANEC	41	4.1	2.8-5.4			
Distant metastasis				23.773	0.000	
Yes	44	5.0	2.7-7.3			
No	92	11.0	9.2-12.8			

CI, confidence interval; NR, not reached; NC, not computable; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; MANEC, mixed adenoendocrine carcinoma.

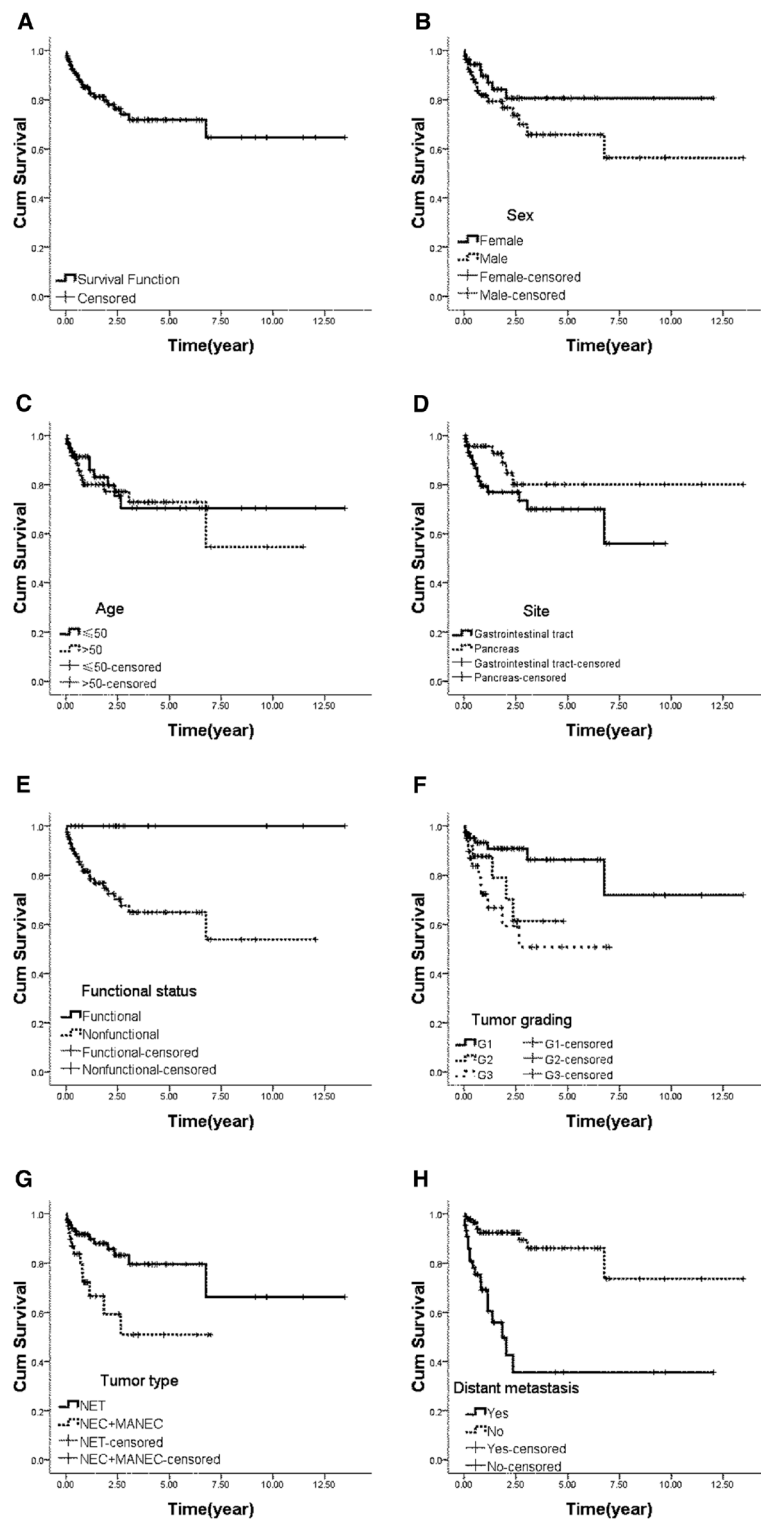
significantly differed from that in our series: Rectum and jejunum/ileum were the most common sites for NENs in the SEER Program tumor registry, pancreas NENs were only the third most common NENs; The pancreas and jejunum/ileum were the most frequent positions in RGETNE; whereas the small intestine was the most frequent sites of origin, followed by the colon and rectum in NRC. These inconsistencies may be due to the racial disparities, as well as the selection bias among population based data and hospital series. So a larger patient population is required to carry on further investigation.

NENs can be classified into functional and non-functional tumors according to the presence or absence of symptoms associated with hormones overproduction [18]. The current study demonstrated that the majority of nonfunctional NENs usually presented with non-specific symptoms, which may give rise to misdiagnosis of the tumors as irritable bowel syndrome or digestive adenocarcinomas. Our study also showed that insulinomas

were the most frequently encountered functional tumors in the pancreas, accounting for 93.1% of pancreatic NENs. No case, however, presented with carcinoid syndrome in this study. Interestingly, the incidence of carcinoid syndrome (10–32%) in the Western population [8,17,19–21] is significantly different from our report, with the fact that ileal tumors account for the vast majority.

Assessments of the locations and extents of GEP-NENs were crucial for management. The present study analyzed imaging methods, which is commonly used in current clinical practice, in this patient population. Conventional imaging procedures include endoscopy, ultrasound, EUS, CT scan, MRI and PET-CT, with detection rates ranging from 77.8 to 98.7%. CT scan was one of the most widely used imaging modalities (123/178) whereas endoscopy promised the highest yields of tumor detection (98.7%). The introduction of EUS provides unique advantages in evaluating the pancreatic biliary system, especially in tumors <1.0 cm in diameter and micrometastasis. The typical EUS patterns of NENs includes rounded, homogeneous, hypochoic, well defined and vascularized masses, with the detection rate of 91.9% in our study, rather comparable to the results achieved in other series [22–24]. Small tumors and liver metastasis (i.e., tumors <0.5 cm in diameter) may be missed, resulting in underestimate of the exact disease extent. No single technique is 100% sensitive and accurate. Therefore, multiple imaging modalities should be combined to detect small, biochemically diagnosed tumors.

Despite the advances in both morphology and biology, the classification of NENs is still under debate. The lack of a uniform classification system for NENs hampers evaluation of therapy and comparison between clinical trials [25]. European Neuroendocrine Tumor Society (ENETS) and the North American Neuroendocrine Tumor Society (NANETS) have published diagnosis standard and pathology reports of NENs in 2009 and 2010 [18,26], respectively. Furthermore, the WHO revised the nomenclature and classification of GEP-NENs in 2010, version 4 [4]. In 2011, China established her own classification system for NENs [5]. Chinese Pathologic Consensus Group suggested the term “Neuroendocrine neoplasm (NEN)” instead of “Neuroendocrine Tumor (NET)” and formulated the classification criteria by the use of Ki-67 index/mitotic rate and histology. The pathologic features of NENs in our hospital were reviewed according to this diagnosis consensus in the current analysis, which to our knowledge, is the first study using the newest consensus. Overall, G1 tumors accounted for 51.5% of 169 available cases, followed by G3 (30.2%) and G2 (18.3%). The occurrence of NET, NEC and MANEC were 69.8%, 27.2% and 3.0%, respectively. The availability of this uniform system for NETs greatly facilitates



**Figure 1** Overall survival (A) Overall survival in all patients. (B) Overall survival by sex. (C) Overall survival by age at diagnosis. (D) Overall survival by site of tumors. (E) Overall survival by functional status. (F) Overall survival by histological grading. (G) Overall survival by tumor type. (H) Overall survival by condition of distant metastasis.

classification of the tumors, evaluation of treatment, and comparison of clinical trials.

In our series, distant disease at initial diagnosis occurred at the rate of 23.0%, which increased to 28.1% during follow up. Liver was the most frequent site tumor involved and the distribution of distant metastasis was wider than that either in SEER or in NRC (18–22%). In RGETNE, however, a significant proportion of patients (44%) with widespread disease were reported compared with our series. The frequency of primary tumor sites associated with distant disease varied in different series: in our cohort, the most common sites was cecum (100.0%), followed by jejunum/ileum (75.0%), gallbladder (50.0%), duodenum (38.5%), Vater's ampulla (33.3%) and stomach (28.0%); in the SEER Registry, the most common site was pancreas (64%), followed by cecum/colon (44%/32%) and jejunum/ileum (30%); and in the RGETNE Registry, it was jejunum/ileum (65%), followed by colon (48%) and rectum (40%). Therefore, jejunum/ileum tumors appear to have a greater propensity for distant metastasis. However, the diversity should be taken into account.

Among the many therapeutic options for NENs, surgery is the treatment of choice. A variety of operations are available to reduce load of tumor and improve survival. The extent of surgical resection depends on the tumor size and origin and approximately 75.9% of patients have undergone a radical surgery. Radiofrequency ablation or TACE is usually adopted to treat liver involvement, accounting for 6.2% of the cases.

Besides surgery, other therapeutic options such as chemotherapy, biological therapy and targeted therapy can be used for NENs. According to the new WHO 2010 classification, well-differentiated NENs are classified as G1 and G2 neuroendocrine tumors (NETs) and poor-differentiated NENs are referred to as G3 neuroendocrine carcinomas (NECs). It has been reported that existing cytotoxic chemotherapy agents have been of limited value for the treatment of well-differentiated gastrointestinal NENs (with response rates 10% ~ 15%) [27–29], but has been the standard of care for well-differentiated metastatic pancreatic endocrine tumors (with response rates 40% ~ 70%) [30–32]. However, chemotherapy is generally considered active in poor-differentiated NENs (with response rates 50% ~ 70%) [33–35]. According to the published documents, several chemotherapeutic regimens are available, most of them are either platinum based or flurouracil based [29,34,36,37]. For the GEP-NEC, platinum-based combination regimens with etoposide or paclitaxel [33,34,36] are recommended. In our cohort, chemotherapy was performed in 23 patients. The most frequently used chemo regimen was etoposide–platinum combination. During follow-up, 3 of them died of tumor progression. It has been noticed that

biological therapy and targeted therapy promise some effect on NENs in recent years [38–43]. Somatostatin analogues are effective therapeutic option for functional neuroendocrine tumors because they reduce hormone-related symptoms [44–46]. They have also been shown to stabilize tumor growth over long periods, even to inhibit tumor growth in patients with well-differentiated metastatic neuroendocrine midgut tumors [40,47,48]. Although the treatment effect of somatostatin analogues on foregut and hindgut tumors remain to be confirmed, 16 patients including 2 patients with functional neuroendocrine tumors and 14 patients with well-differentiated metastatic GEP-NENs received long-term administration of octreotide LAR at a dose of 20–40 mg monthly in our study.

The prognosis of GEP-NENs is more favorable than that of the adenocarcinomas of the digestive system. The overall 5-year survival rate in our series was 54.5%, rather comparable to that of SEER or NRC registry [2,3,6] (50–59%), but it was lower than that in some European countries [7,9] (75–79%). The inconsistencies of survival rates may be due to the racial and geographical disparities. We also proved that prognosis differed statistically according to functional status, pathological grading and classification. As the great majority of functional tumors were insulinomas which are benign in most cases in our study, that may lead to the conclusion that functionality may be a favorable prognostic marker. The result obtained above may be caused by small sample in this series. We also confirmed that metastasis represented a worse outcome with a mean survival of 5.0 years ( $P = 0.000$ ). Multivariate analysis was not done due to the small size of our series. Therefore, further evaluation in a larger patient population is required to estimate the independent prognostic factors of GEP-NENs.

A broad range of this heterogeneous tumors was reviewed in the current study, which to our knowledge, is the first report using the latest pathological diagnosis consensus of these tumors. We also confirmed that GEP-NENs may originate from any part of the digestive system, and the majority of them are nonfunctional tumors with non-specific symptoms. Endoscopy and radiographic examination play an important role in tumor detection. However, final diagnosis should be based on pathological detection. The prognosis of these tumors was more favorable compared with gastrointestinal carcinomas. Nonetheless, the outcome was extremely poor for patients with high grading tumor and distant metastasis. Further understanding of the molecular mechanisms should facilitate management of the disease. Early diagnosis is crucial for radical resection before development of local invasion or distant disease, and interdisciplinary cooperation is the direction of future.

## Conclusions

Nonfunctional tumors with non-specific symptoms account for the majority of GEP-NENs. Diagnosis depends on pathological classification. Multidisciplinary treatments could help improve the outcome.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

WYH and LY contributed equally to this work; WYH and LY: Collection and/or assembly of data, Data analysis and interpretation, Manuscript writing; LY and XL: Pathological data collection and analysis; WJH: Collection of clinical data; Chen J and Chen MH: Conception and design, Financial and administrative support, manuscript editing. All authors read and approved the final manuscript.

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