Correlation between clinicopathological characteristics and the clinical prognosis of patients with gastroenteropancreatic neuroendocrine tumors

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Received July 12, 2023; Accepted September 5, 2023

DOI: 10.3892/mco.2023.2681

Abstract. Gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) are one of the most common types of NETs, accounting for 65-75% of all NETs. However, epidemiological characteristics of patients with GEP-NETs in China are still lacking. The present retrospective study aimed to investigate the local epidemiology of GEP-NETs and assess the prognostic factors in China. The data of 267 patients with GEP-NETs who were admitted to the First Affiliated Hospital of Bengbu Medical College (Bengbu, China) and the Affiliated Hospital of West Anhui Health Vocational College (Lu'an, China) were retrospectively reviewed. The clinical and pathological characteristics of the patients, as well as follow-up information, were collected, and the 5-year survival rate was calculated. Kaplan-Meier curves and log-rank analysis were used to analyze the prognostic factors. The stomach (100/267; 37.5%) was the most common site of GEP-NETs and the liver (25/39; 64.1%) was the most common metastatic site. A total of 166 (62.2%) and 219 (82.0%) patients had positive results for chromogranin A (CgA) and synaptophysin (Syn), respectively. The percentage of patients with tumor grade G1, G2 and G3 was 33.3, 21.0 and 45.7%, respectively. The 5-year overall survival rate was 79.7%, and the age, tumor site, distant metastasis and tumor grading upon diagnosis were all prognostic factors. In conclusion, the present case series investigated the epidemiology and prognostic factors of GEP-NETs in China. CgA and Syn could be used as diagnostic markers for NETs and the stomach was the most common primary tumor site. Lymph node metastasis, tumor site, distant metastasis and tumor grading were important prognostic factors.

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Key words: gastroenteropancreatic neuroendocrine tumor, clinical and pathological characteristics, prognostic factors

Introduction

Neuroendocrine neoplasms (NENs) compose a class of heterogeneous tumors originating from the neuroendocrine system and can occur in multiple organs and tissues, such as the esophagus, gastrointestinal tract, pancreas, lungs and bronchi, among which the digestive system is the most common (1). The incidence and prevalence of NENs has increased markedly over the past 30 years, and the incidence of NENs was estimated to be 5.25 per 100,000 individuals up to 2022, with gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) accounting for 65-75% of all NENs, according to data from the US Surveillance, Epidemiology and Final Results Database (SEER) (2). According to national databases and patient registration center data, the incidence rate of GEP-NENs in the United States was ~3.56 per 100,000 individuals up to 2021 (3). In the UK, the incidence rate of NENs in 2018 was ~9 per 100,000 individuals. It is worth noting that the incidence rate of pancreatic and rectal NENs showed a significant increase in the past 10 years. In Japan, the incidence rate of GEP-NENs in 2016 was reported to be 3.53 per 100,000 individuals. The most common primary site for GEP-NENs in Japan was the rectum, accounting for 53.0% of the total GEP-NEN cases, followed by the pancreas (20.0%) and stomach (13.0%) (4). NETs in the stomach are rare, but a recent study found that their incidence has undergone a significant increase (5). Neuroendocrine carcinomas (NECs) include small cell carcinoma and large cell neuroendocrine cancer. The cells of small cell carcinoma are generally small (typically >3 lymphocytes in volume) and their appearance resembles lymphocytes with sparse cytoplasm. Small cell carcinoma of the nucleus deep-dyed and the nucleoli are not visible, while at the same time, its mitotic figures are easily seen, with nest clusters or diffuse distribution, often accompanied by necrosis. NENs are characterized by the ability to secrete and store different peptides and neuroamines. It is considered that GEP-NETs can produce peptide-active substances that can cause specific hormonal syndromes, such as skin flushing, diarrhea, asthma and heart valve disease (6). At present, most GEP-NENs

are recognized as non-functional tumors (7). Owing to the fact that GEP-NENs are relatively rare, they lack specific symptoms and hence are difficult to diagnose.

To the best of our knowledge, at present, there are only a few related studies about GEP-NENs in China (8,9). Therefore, the present retrospective study retrieved the data collected from 267 patients with NETs between September 2005 and October 2017. These patients were diagnosed with GEP-NEN at the First Affiliated Hospital of Bengbu Medical College (Bengbu, China) and the Affiliated Hospital of West Anhui Health Vocational College (Lu'an, China), and the clinical and pathological features of GEP-NEN, along with its prognostic factors, were investigated in the present study.

Materials and methods

Objective of study. Data from 267 patients diagnosed with GEP-NEN at the First Affiliated Hospital of Bengbu Medical College and the Affiliated Hospital of West Anhui Health Vocational College were retrieved and analyzed. The diagnostic criteria were based on the consensus opinion on pathological diagnosis of gastrointestinal pancreatic NEN established in China (10), the National Cancer Network Guide of the United States (11) and the consensus of the European NEN Association (12,13).

Methods of data collection. The histopathological examination results, patients' age, tumor locations, pathological examination results, maximum diameters of the tumors, World Health Organization (WHO) grade (2), the occurrence of lymph node and distant metastases, the results of immunohistochemical analysis of chromogranin A (CgA) and synaptophysin (Syn) (14) were collected.

Statistical analysis. The SPSS v22.0 (IBM Corp.) statistical software package was used for statistical analysis. The case data is presented in the form of number of cases and percentage. The overall survival time is presented in the form of the mean ± SD. The Kaplan-Meier method and log-rank test were used to analyze potential prognostic factors. The log-rank test was used for the univariate analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical and pathological characteristics. Out of 267 GEP-NEN cases, 100 (37.5%) were located in the stomach, 81 (30.3%) in the colorectal tract, 51 (19.1%) in the esophagus, 22 (8.2%) in the pancreas and the remaining 13 (4.9%) in other parts of the digestive tract, such as the duodenum, jejunum, ileum and appendix. Among the patients, there were 175 men and 92 women. The ratio of men to women was 1.9:1. The age range of the patients was between 20 and 86 years. The mean ages of the patients with tumors in the stomach, colorectal tract, esophagus, pancreas and other parts of the digestive tract were 61.7, 63.5, 65.4, 49.9 and 63.9 years, respectively. The mean ages of the patients with pancreatic NETs was lower than that of patients with tumors located in other parts of the digestive system. There were 147 patients with a tumor diameter ≤2 cm and 120 patients with a tumor diameter >2 cm. According to the WHO classification, there were 89 (33.3%), 56 (21.0%) and 122 (45.7%) cases of NET at G1, G2 and G3, respectively. In these cases, 135 patients (50.6%) had lymph node metastasis and the lowest rate of lymph node metastasis was in the pancreas (27.3%). Among all the patients, 73 (27.3%) had distant metastases and 35 (47.9%) of these 73 had liver metastases, so the liver was the most likely to metastasize. Specific clinical and pathological information can be found in Table I.

Immunohistochemical analysis of the expression of CgA and Syn. The volume of large cell neuroendocrine cancer cells was often >3 times larger than that of the lymphocytes, and it was very rich in cytoplasm and nucleoli. At the same time, cell mitosis was evident and the cells were arranged in a daisy group or diffuse distribution, often accompanied by necrosis (Fig. 1A and B). A total of 166 patients (62.2%) were CgA-positive, while 219 (82.0%) patients were Syn-positive. The results of the CgA and Syn immunohistochemical staining in different tumor tissues are reported in Table II.

Univariate analyses of overall survival (OS). Follow-up data showed that the OS time for patients with lymph node metastases (32.6±13.7 months) was lower than that for patients without lymph nodes metastases (51.6±12.1 months) (log-rank=53.782, $P<0.001$; Table III; Fig. 2A). The total OS time of patients with a tumor diameter >2 cm (37.4±14.5 months) was significantly lower than that of patients with a tumor diameter ≤2 cm (52.3±13.7 months) (log-rank=31.156, $P<0.001$; Table III; Fig. 2B). Similarly, patients with distant metastases (37.7±14.7 months) had significantly lower OS times than those without distant metastases (52.2±13.5 months) (log-rank=55.604, $P<0.001$; Table III; Fig. 2C). With regard to the WHO classification, the OS time of patients with G1 disease (49.7±14.7 months) was significantly higher than that of patients with G2 disease (37.5±14.9 months) and NEC (31.6±10.6 months) (log-rank=38.353, $P<0.001$; Table III; Fig. 2D). In the univariate analysis, OS had no significant association with other clinicopathological features, as detailed in Table III.

Discussion

NEN is a rare type of tumor, accounting for ~2% of digestive tract malignant tumors. Previous studies showed that the incidence of NEN in the United States from 1973-2004 increased by 3.8 times, while the NEN detection rate also showed an upward trend in other countries and domestic regions (15,16). The improvement in the NEN detection rate may also be related to the improvement in diagnostic techniques such as imaging and immunohistochemistry, and the popularization of endoscopy. NEN can occur in several organs and, due to the distribution of a variety of neuroendocrine cells, the digestive system is the most common NET site (17). To the best of our knowledge, due to the lack of specificity of clinical symptoms of GEP-NEN, only a few studies have been performed in China or other countries, and there are not enough international reports on GEP-NEN in Asia (8,9,15,16). Therefore, the present study retrospectively reviewed and analyzed the clinical data collected from

Table I. Clinical and pathological data of GEP-NETs in different parts.

	GEP-NETs, n				
Pathological features	Esophagus	Stomach	Colorectal tract	Pancreas	Others[a]
Sex					
Male	33	73	47	11	11
Female	18	27	34	11	2
Age, years					
≥60	41	65	28	8	8
<60	10	35	53	14	5
Tumor diameter, cm					
≤2	28	43	54	15	7
>2	23	57	27	7	6
WHO grade					
G1	10	21	49	6	3
G2	16	23	9	6	2
G3	25	56	23	10	8
Lymph node metastasis					
Yes	29	55	39	6	6
No	22	45	42	16	7
Distant metastasis					
Liver	10	8	9	6	2
Lungs	5	2	4	2	1
Mediastinum	11	2	1	0	1
Others[b]	1	3	2	1	2

[a]Excluding esophagus, stomach, colorectal tract, pancreas and other parts of the digestive tract, such as the duodenum, jejunum, ileum and appendix. [b]Other distant metastases of organs, such as the lumbar spine, bones, adrenal gland and pericardium. GEP-NET, gastroenteropancreatic neuroendocrine tumor; WHO, World Health Organization.

Table II. Immunohistochemical staining showing CgA- and Syn-positive results in different gastroenteropancreatic neuroendocrine tumor regions.

	CgA-positive		Syn-positive	
Tumor location	Number of cases	Percentage	Number of cases	Percentage
Esophagus	30	58.8	32	62.8
Stomach	73	73.0	89	89.0
Colorectal tract	44	54.3	73	90.1
Pancreas	13	59.1	18	81.8
Others[a]	6	46.2	7	53.9

[a]Excluding esophagus, stomach, colorectal tract, pancreas and other parts of the digestive tract, such as duodenum, jejunum, ileum and appendix. CgA, chromogranin A; Syn, synaptophysin.

patients diagnosed with NEN of the digestive system at two hospitals to provide real-world evidence as a reference for the clinical management of this disease.

The size of the study population, sex distribution (male/female ratio) and results of the present study are in agreement with other previous studies performed in China. One previous study suggested that the differences in sex distribution for tumor sites have statistical significance (8), which is consistent with the results of the present study, although these were not statistically analyzed. In China, the gastrointestinal tract and pancreas are the most common sites of NEN, accounting for 65-75% of the total number of NEN cases. In developed countries, GEP-NEN occurs in the order of the rectum, jejunum, pancreas and stomach (18). In one study, the incidence of NENs in the small intestine was 44.7%, followed by 19.6% in the rectum, 16.7% in the appendix, 10.6% in the colon and 7.2% in the stomach, with 11,427 patients with NEN analyzed (19). In the present study, 37.5% (100/267) of the tumors occurred in the stomach, followed by 30.3% in the colorectal tract, 19.1% in the esophagus, 8.2% in the pancreas and 4.9% in other parts of the digestive tract. The present study showed that the stomach and colorectal tract are the most common sites of GEP-NEN, in agreement with previous similar studies. The differences in the prevalence of GEP-NEN in Chinese patients and those of different ethnicities may be related to environmental, genetic and ethnic differences. Previous studies found that differences in the incidence of GEP-NEN between different databases are

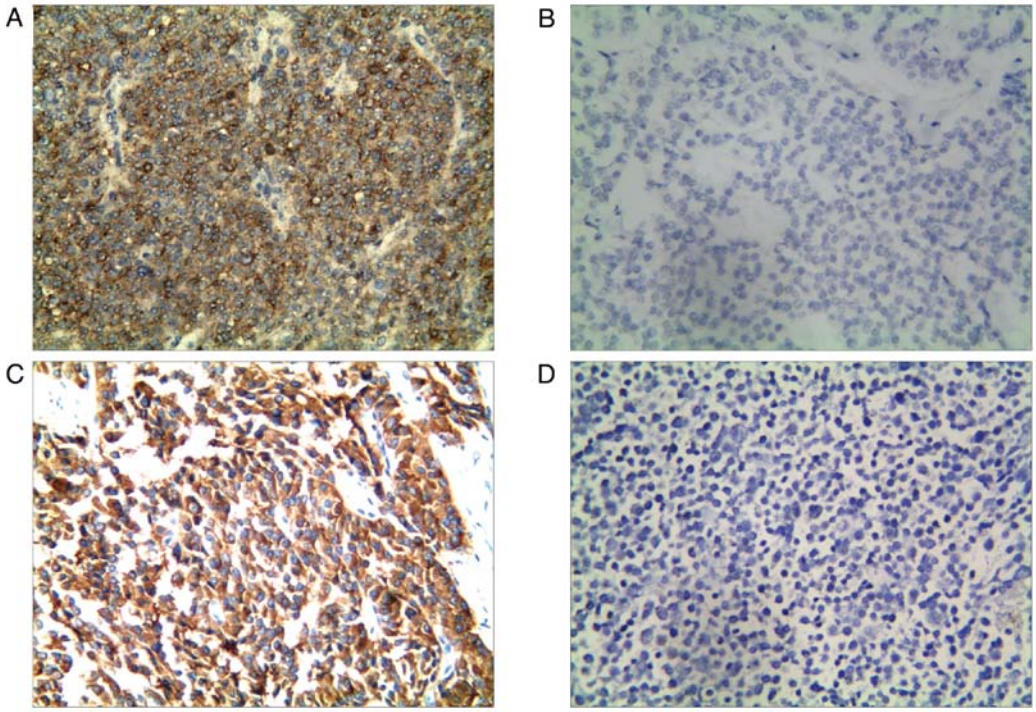

Figure 1. Results of immunohistochemical expression of CgA and Syn in the digestive system. (A) Positive staining of CgA, (B) negative staining of CgA, (C) positive staining of Syn and (D) negative staining of Syn in the tissue of digestive system (x400 magnification).

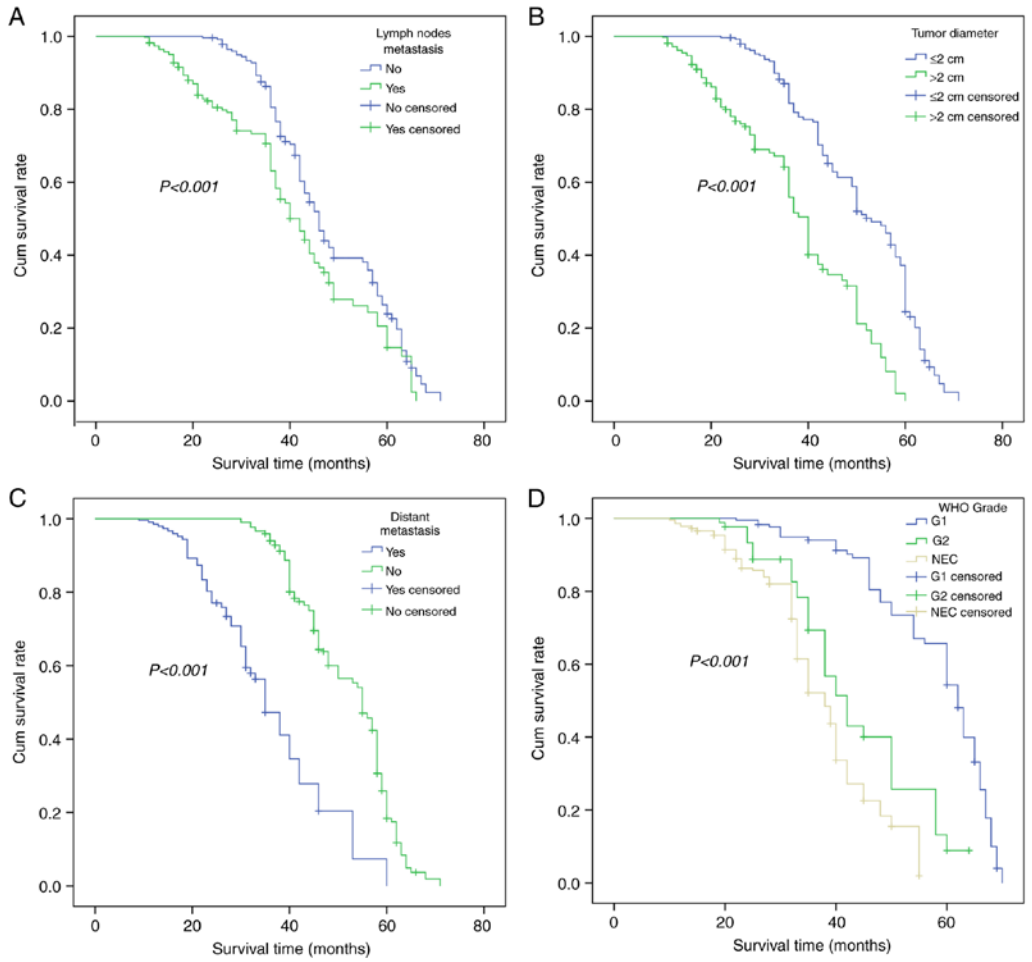

Figure 2. Kaplan-Meier analysis of the survival rate of patients with gastroenteropancreatic neuroendocrine tumors. Overall survival of all patients in relation to (A) lymph node metastasis (log-rank, 53.782; P<0.001), (B) tumor diameter (log-rank, 31.156; P<0.001), (C) distant metastasis (log-rank, 55.604; P<0.001) and (D) WHO classification (log-rank, 38.353; P<0.001). WHO, World Health Organization; NEC, neuroendocrine carcinoma; cum, cumulative.

Table III. Results of univariate analysis of OS time.

Variable	n	OS time (mean ± SD)	Log-rank	P-value
Sex			0.271	0.539
Male	175	45.6±15.3		
Female	92	42.6±15.5		
Age, years			0.256	0.610
≥60	150	47.5±14.5		
<60	117	50.7±14.5		
Tumor diameter, cm			31.156	<0.001
≤2	147	52.3±13.7		
>2	120	37.4±14.5		
Tumor location[a]			2.031	0.362
Esophagus	51	50.9±14.1		
Stomach	100	42.4±16.2		
Colorectal tract	81	40.2±15.2		
WHO grade			38.353	<0.001
G1	80	49.7±14.7		
G2	44	37.5±14.9		
NEC	143	31.6±10.6		
Lymph node metastasis			53.782	<0.001
Yes	135	32.6±13.7		
No	132	51.6±12.1		
Distant metastasis			55.604	<0.001
Yes	73	37.7±14.7		
No	194	52.2±13.5		

[a]n=232 as only the locations with the majority of cases are presented. OS, overall survival; WHO, World Health Organization; NEC, neuroendocrine carcinoma.

related to sex and ethnic factors. NETs of the ileum, rectum and lung are more common in Europe and the United States, whereas in Asia, rectal, stomach and pancreatic tumors occur frequently (20-22).

The present study found that the patients with tumors in the stomach, colorectal tract, esophagus, pancreas and other parts of the digestive system had an mean age of 61.7, 63.5, 65.4, 49.9 and 63.9 years, respectively. Moreover, the average age of patients with pancreatic NETs was lower than that of patients with tumors located in other parts of the digestive system, which is more consistent with previous similar studies. One previous study indicated that early esophageal NETs can be associated with distant metastasis and rapid progress (23). Furthermore, gastric NETs, compared with gastric adenocarcinomas, are more prone to lymph node metastasis, liver metastasis and tumor emboli (24). In the present study, the rate of lymph node metastasis of the esophagus, stomach, colorectal tract, pancreas and other regions were 56.9, 55.0, 48.1, 27.3 and 85.7%, respectively. This result is different from that of the previous studies performed in China. This difference could be due to regional factors or it may be caused by the bias generated by the small number of patients with tumors in the pancreas and other regions of the digestive system. With regard to the relationship between tumor diameter and metastasis, a previous study proposed that the metastasis rate for NETs with a diameter <2 cm was 14.2%, whereas that for NETs with a diameter >2 cm was 38.4% (25). A previous study classified rectal NETs according to different pathological grades and found that the proportion of patients with a tumor diameter >2 cm with grades G1, G2 and G3 was 23, 81 and 50%, so that a tumor diameter >2 cm could be used as a metastatic prognostic factor with good specificity and sensitivity (9). Concerning the distant metastasis rate of GEP-NEN, the present study is different from the domestic reports, which may be related to the small sample size and incomplete case data. The present study also discovered that, in the pancreas, the majority of NENs were NETs with a lower level of malignancy. The proportion of NETs in the pancreas was relatively low compared with NENs in other regions of the body. This indirectly suggested that there may be variations in the pathological characteristics of NETs in different locations, including differences in the level of tumor malignancy. Although a GEP-NEN has typical histopathological features, it is usually indistinguishable from adenocarcinoma and is often diagnosed as adenocarcinoma with neuroendocrine differentiation in clinical practice. To avoid any confusion about diagnosis and treatment, the use of the term 'adenocarcinoma with neuroendocrine differentiation' should be avoided in the diagnosis, while the use of immunohistochemical staining and other methods to improve the accuracy of

diagnosis is recommended (12,26). According to the relevant foreign guidelines (11,13), a diagnosis of GEP-NEN should include neuroendocrine markers, such as Syn and CgA, and proliferation index markers, such as Ki-67/MIB E3 ubiquitin protein ligase 1 (27). CgA is a chromaffin particle present in the secretory vesicles of neuroendocrine cells and neurons, but not all neuroendocrine cells are present in such vesicles. CgA is currently recognized as a valuable GEP-NEN tumor marker. Syn is a glycoprotein located in presynaptic vesicles, and the vast majority of NEN cells can express Syn (28).

CgA and Syn are both useful markers for the diagnosis of NETs. However, both CgA and Syn have some limitations. CgA is not specific to NETs, as it can be increased in other conditions such as pancreatic cancer and renal failure (29,30). Additionally, CgA levels can be affected by certain medications, such as proton pump inhibitors, which can lead to false-positive results (31,32). Syn is also not specific to NETs, as it can be elevated in other conditions such as multiple sclerosis and Parkinson's disease. Additionally, Syn levels can be affected by certain medications, such as antidepressants, which can lead to false-positive results (29,30). The NETest is a new test developed to overcome the limitations of CgA and Syn. The test is a combination of three biomarkers (CgA, Syn and neuron-specific enolase) that is specific to NETs and are not affected by associated NET medications (33). The NETest has been shown to have superior diagnostic properties, and prognostic and predictive value compared to traditional analytes (34). Additionally, the NETest is more cost-effective than traditional tests, making it an attractive option for the diagnosis of NETs. However, the NETest also has some potential drawbacks, as it is not available in all countries and it is not yet widely used in clinical practice (35). Additionally, the NETest is not as sensitive as CgA and Syn, meaning that it may not detect all NETs. Finally, the NETest is not specific to NETs, as it can be elevated in other conditions such as pancreatic cancer and renal failure (36).

In the present study, the overall positive rate of Syn was significantly higher than that of CgA (62.0 vs. 62.2%) in GEP-NENs and the results were consistent with the results obtained from previous studies (14,29). Moreover, the positive rate of colorectal Syn was 90.12%, while the positive rate of CgA was only 54.32%, mainly due to the high expression of CgB in sigmoid colon and rectal tumors; however, conventional immunohistochemistry antibodies have a lower detection rate for this substance, resulting in a lower overall detection rate of CgA in colorectal tumors. Syn can be used as the first detection marker of intestinal NEN and its expression in the intestine is more stable (37).

In summary, the stomach is the most common GEP-NEN primary site. Lymph node metastasis, tumor site, distant metastasis and tumor grading are important prognostic factors. Although most of the GEP-NENs have typical histopathological features, the diagnosis also needs to refer to the results of immunohistochemical staining, and the positive expression of CgA and Syn is helpful to diagnose GEP-NENs.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CH conceived and designed the study. XL, YY, XW and JF acquired data. DF, XL, YY, XW and JF analyzed and interpreted the data. XL, YY XW and JF provided clinical material support and analyzed clinicopathological data. DF and XL drafted the manuscript. DF and XL confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study does not involve ethical issues and does not require approval from the ethics committee. Patient information and data are sourced from follow-up and retrospective analysis.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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