An 11-year retrospective study: clinicopathological and survival analysis of gastro-entero-pancreatic neuroendocrine neoplasm

Hua Liu, MD,1,2, Rongli Xie, MD,1,3, Zhifeng Zhao, MD,3, Dan Xu, MD,3, Kaige Yang, MD,3, Min Ding, MD,3, Dan Tan, MD,3, Wenqiang Liao, MD,2, Xujie Han, MD,2, Jun Zhang, MD,3, Dongjie Shen, MD,3, Jianmin Yuan, MD,3, Zhiwei Xu, MD,1,∗, Jian Fei, MD, PhD1,∗

Abstract
To investigate the clinicopathological characteristics and relevant prognostic factors of gastro-entero-pancreatic neuroendocrine neoplasm (GEP-NEN), to improve our understanding of GEP-NEN. This was a retrospective analysis of 155 patients (average age 53.7 ± 13.6 years) pathologically diagnosed with GEP-NEN. We analyzed the clinicopathological characteristics, treatment, and prognostic factors of GEP-NEN.

The most common primary site was the pancreas (41.9%), followed by the rectum, stomach and duodenum. Most cases were nonfunctional GEP-NENs (149/155) with nonspecific symptoms. TNM stage and histological grade were determined by the latest criteria. Surgical resection was the mainstay of treatment in 150 patients, and 22 patients received chemotherapy under different circumstances. A total of 130 patients were followed up for a median of 44 months, and 1-year and 3-year survival rates were 82.3% and 72.3%, respectively. According to univariate and multivariate analysis, incidental diagnosis, maximum tumor diameter, tumor stage, lymph node and distant metastasis, TNM stage, and histological grade were significantly correlated with overall survival, but histological grade was the only factor confirmed as an independent prognostic factor for long-term survival of GEP-NEN.

GEP-NEN, with an increasing trend in incidence, occurred most frequently in the pancreas. Nonfunctional tumors with nonspecific symptoms comprised the majority of cases. The main treatment was surgical resection. Histological grade was confirmed as the only independent prognostic factor.

Abbreviations: ACTH = adrenocorticotropic hormone, AJCC = American Joint Committee on Cancer, GEP-NEN = gastro-entero-pancreatic neuroendocrine neoplasm, NEN = Neuroendocrine neoplasm, SEER = Surveillance Epidemiology and End Results, TACE = trans-catheter arterial chemo-embolization, WHO = World Health Organization.

Keywords: clinicopathological characteristics, gastro-entero-pancreatic neuroendocrine neoplasm, neuroendocrine neoplasm, prognostic factors, survival analysis

1. Introduction
Neuroendocrine neoplasm (NEN), a class of heterogeneous tumor that originates from the diffuse neuroendocrine system, has varied biological behavior and clinical manifestations throughout the body. Neuroendocrine cells, which can express specific neuroendocrine markers, generate biogenic amines such as 5-serotonin and prostaglandin, or hormones such as gastrin and insulin, which can cause complicated symptoms. Oberndorfer first described NEN as carcinoid in 1907, because of its peculiar characteristics such as indolent growth, lower
invasiveness and favorable prognosis compared with other malignancies. It was not until 2000 that the term NEN was used officially by the World Health Organization (WHO) to substitute for carcinoid. Traditionally, NEN was considered to be a rare disease, but recent reports indicate a significant increase in its incidence. According to the US Surveillance Epidemiology and End Results database, the annual age-adjusted incidence of NEN rose from 1.09/100,000 in 1973 to 5.25/100,000 in 2004. Gastro-entero-pancreatic (GEP)-NEN accounts for 65% to 75% of all NENs and ranks second behind colorectal cancer in digestive system neoplasms. Traditionally, NEN was considered to be a rare malignant (GEP-NEN) for a long time, which is probably due to the wide distribution, atypical clinical symptoms, and unawareness of clinicians. As a result, it has always been too late for effective treatment when patients were finally diagnosed. Early detection and diagnosis mainly depend on endoscopy, imaging, and most importantly, pathological examination. However, there has been a poor diagnostic rate of gastro-entero-pancreatic neuroendocrine neoplasm (GEP-NEN) for a long time, which is probably due to the wide distribution, atypical clinical symptoms, and unawareness of clinicians. As a result, it has always been too late for effective treatment when patients were finally diagnosed.

We retrospectively analyzed the clinicopathological features of 155 cases of GEP-NEN and investigated the correlation between various factors and prognosis, to improve our understanding for early diagnosis and better treatment.

2. Patients and methods

2.1. Patients

A total of 155 patients (94 male and 61 female) were enrolled, with an average age of 53.7 ± 13.6 years. All patients were pathologically diagnosed as GEP-NEN in our hospital from February 1, 2003 to February 28, 2014 and were followed up for at least 3 years, which ended on February 28, 2017. All the procedures were implemented in accordance with the principles of the Declaration of Helsinki. Since this was a retrospective case study, patient consent was waived by our Institutional Ethics Committee.

2.2. Methods

The clinicopathological characteristics of GEP-NEN collected were as follows: age at diagnosis, gender, primary site, clinical manifestations, pathological features, maximum diameter and stage of the tumor, presence of lymph node and distant metastasis at diagnosis, TNM stage and grade, and treatment details. Besides, follow-up information was analyzed to explore potential prognostic factors. Follow-up information was obtained through telephone calls, and those who could not be contacted were considered for withdrawal.

2.3. Grading and staging criteria

Histological grading. According to the WHO 2010 Classification, tumors with a Ki-67 index <2% or mitotic rates <2/10 HPF as G1; Ki-67 index 3% to 20% or mitotic rates 2–20/10 HPF as G2; and >20% or 20/10 HPF as G3. In addition, the higher classification would be adopted if the 2 indexes were inconsistent. For mixed adenoneuroendocrine carcinoma, both the high-grade NEN and the adenocarcinoma proportion should exceed 30% of the lesion.

TNM staging. The patients were staged according to the latest criteria, 2016 American Joint Committee on Cancer (AJCC) criteria (8th edition) for TNM classification.

2.4. Statistical analysis

Statistical analysis was performed using SPSS version 19.0. Measurement data were described as mean ± standard deviation or median. Kaplan–Meier and log-rank test were used for univariate analysis, and for those who presented P < .05 in the univariate analysis, Cox-proportional hazard model was applied for multivariate analysis. All tests were 2-sided, and P < .05 was considered statistically significant.

3. Results

3.1. Patients’ characteristics

The detailed clinicopathological characteristics of all patients are listed in Table 1. We identified 155 patients pathologically diagnosed with GEP-NEN during an 11-year period. Figure 1 showed the distribution of new cases during the study period. A male predominance (94/155, 60.6%) was observed among these patients, with a mean age of 54.65 ± 13.31 years at diagnosis, compared to 52.23 ± 14.11 years in female patients. The peak age group at diagnosis was 50 to 60 years. The commonest primary site was the pancreas (41.9%, n = 65), followed by the rectum (24.5%, n = 38), stomach (18.7%, n = 29), duodenum (9.0%, n = 14), colon (3.9%, n = 6), appendix (1.3%, n = 2) and small intestine (0.7%, n = 1) (Fig. 2). Most GEP-NENs were nonfunctional (96.1%, n = 149), and the remaining functional GEP-NENs that all occurred in the pancreas included 4 insulinomas and 2 adrenocorticotrophic hormone (ACTH)-secreting tumors. Patients with nonfunctional GEP-NENs generally showed nonspecific gastrointestinal symptoms, which included abdominal pain, hematochezia, bowel habit alteration, and emaciation. While functional tumors such as insulinoma showed hypoglycemia and ACTH-secreting tumors had Cushing syndrome. Of the 155 GEP-NEN cases, 47 patients (30.3%) were accidentally found when they had imaging tests or endoscopy performed for routine health examination and cancer screening.

3.2. Pathological characteristics

All cases were available for analysis of T-staging, which was decided by tumor size and degree of infiltration according to surgery or ultrasonic endoscope records. T1 accounted for 53 (34.2%) cases, while T2, T3, and T4 accounted for 32 (20.6%), 30 (19.4%), and 40 (25.8%), respectively. In addition, 42 (27.1%) patients had lymph node metastases at initial diagnosis, and 15 (9.7%) had distant metastases, which consisted of 12 liver metastases, 2 multiple metastases (liver–bone and lung–pelvis metastasis), and 1 lung and 1 spinal metastasis. Cases with distant metastasis increased to 40 (25.8%) during follow-up. According to the newest AJCC TNM staging criteria, 42 (27.1%) patients were diagnosed as stage I, 51 (32.9%) as stage II, 47 (30.3%) as stage III and 15 (9.7%) as stage IV. In addition, among 149 cases that were classified based on the 2010 WHO grading classification, 74 (49.7%) were classified as grade 1, 25 (16.8%) as grade 2, and 50 (33.6%) as grade 3. There were 6 cases of mixed adenoneuroendocrine carcinoma: 4 in the stomach, and 2 each in the pancreas and colon. All 6 of these were at least stage III with unfavorable prognosis. The distribution of TNM staging and grading of each primary site are shown in Figure 3. In addition to staging and grading information collected from surgical samples, we analyzed immunohistochemical characteristics of 134 cases that were available. A total of 126 patients (94.0%) stained
positive for synaptophysin, 111 (82.8%) for cytokeratin, 106 patients (79.1%) for chromogranin A and neuron-specific enolase, and 74 (55.2%) for CD56. Pathological details are shown in Table 1.

### 3.3. Treatment

After initial diagnosis, 150 patients (96.8%) underwent surgical resection, before which 3 patients received neoadjuvant chemotherapy, and postoperative chemotherapy was performed in 17 patients. Among those who did not accept surgery, 2 and 1 patients could not tolerate surgery due to advanced cancer and received chemotherapy and targeted therapy, respectively, while the other 2 refused any therapy for unknown reasons. Moreover, trans-catheter arterial chemo-embolization (TACE) was applied to 3 patients who had liver metastasis.

### 3.4. Survival analysis

Overall survival during follow-up period is shown in Figure 4. In our study, 130 patients in this cohort received long-term follow up with a median duration of 44 months (range: 0–164 months),
while 25 patients were lost to follow-up. Mean survival time was 108 ± 9 months (95% confidence interval: 89–126 months), while the median survival time was not available during the observation period. The estimated 1-year and 3-year survival rate was 82.3% (107/130) and 72.3% (94/130), respectively. Furthermore, the overall 5-year survival rate for patients followed up for at least 60 months (n=51) was 51.0% (26/51). Thirty-seven deaths occurred during the follow-up.

Figure 2. The primary tumor site in all cases. A total of 155 cases was analyzed, and the pancreas was the commonest primary site.

Figure 3. Distribution of TNM stage and histological grade in different primary sites.
period, and tumor progression was the most frequent cause of mortality (73.0%, n = 27). Nine patients (24.3%) died as a result of postoperative complications and one committed suicide as a result of depression for postoperative tumor progression.

Univariate analysis was performed using patients’ age (<55 years as the cut-off point), gender, primary tumor site (pancreas versus gastrointestinal tract), tumor functionality, incidental diagnosis, maximum diameter, tumor stage, presence of lymph node and distant metastasis at diagnosis, histological grade according to the 2010 WHO classification, as well as TNM stage according to 2016 AJCC criteria (8th edition) to identify potential prognostic factors of GEP-NEN. Overall survival was significantly greater in patients with maximum tumor diameter < 30mm, lower tumor stage, negative metastasis, and lower grade and TNM stage. These factors were significant prognostic factors for survival (Table 2). A multivariate model was applied to analyze these independent prognostic factors for survival. According to the analysis, only histological grade (P = .041) was confirmed as an independent prognostic factor for survival in patients with GEP-NEN (Table 2). Kaplan–Meier survival curve of histological grade is shown in Figure 5.

### 4. Discussion

This retrospective study analyzed the clinicopathological characteristics of 155 patients confirmed with GEP-NEN, and identified several variables as normal or independent prognostic factors for long-term survival. The overall prevalence and

### Table 2

| Survival time, month | Univariate | Multivariate |
|----------------------|------------|-------------|
|                      | Mean       | Median      | P  | 95%CI  | P  | HR (95%CI) |
| All patients         | 108        | NR          | .12 | 89.2–125.9 | .531 | 0.7 (0.2–2.1) |
| Gender               |            |             | .112 | 79.6–122.9 | .579 | 1.4 (0.4–7.7) |
| male                 | 101        | NR          | 73.5–104.5 | 99.8–114.6 | 5.90–102.5 | <.001 |
| female               | 98         | NR          |                   | 94.0–114.3 | 48.3–92.9 | .002 |
| Age                  |            |             | .147 | 76.9–101.4 | .359 | 1.7 (0.5–5.5) |
| <55                  | 89         | NR          | 61.2–123.2 | 64.1–89.1 | 85.6–132.8 | .654 |
| ≥55                  | 92         | 82          |                   |                   |               |
| Primary site         |            |             | .923 | 36.7–101.6 | .263 | 1.7 (0.7–4.1) |
| pancreas             | 77         | NR          | 93.9–128.9 | 36.7–101.6 | 93.9–128.9 | .046 |
| GIT                  | 109        | NR          |                   |                   |               | .531 |
| Functionality        |            |             |                   | 73.2–100.6 |                   | .531 |
| functional           | 69         | NR          | 74.5–119.9 | 74.5–119.9 | 74.5–119.9 | .732 |
| nonfunctional        | 111        | 82          |                   |                   |               | .732 |
| Incidental diagnosis |            |             | .068 | 73.2–100.6 | .531 | 0.7 (0.2–2.1) |
| yes                  | 87         | NR          | 99.8–114.6 | 99.8–114.6 | 99.8–114.6 | <.001 |
| no                   | 97         | 88          | 59.0–102.5 | 59.0–102.5 | 59.0–102.5 | .813 |
| Maximum diameter     |            |             | <.001 | 94.0–114.3 | .359 | 1.7 (0.5–5.5) |
| <30 mm               | 107        | NR          | 48.3–92.9 | 48.3–92.9 | 48.3–92.9 | .002 |
| ≥30 mm               | 81         | 82          |                   |                   |               | .002 |
| Tumor stage          |            |             | .001 | 18.4–64.2 | .263 | 1.7 (0.7–4.1) |
| T1 and T2            | 104        | NR          | 98.9–134.4 | 18.4–64.2 | 98.9–134.4 | .001 |
| T3 and T4            | 71         | 49          | 98.9–134.4 | 29.7–58.0 | 98.9–134.4 | .001 |
| Distant metastasis   |            |             | .159 | 120.4–150.7 | .031 | 3.0 (1.1–8.0) |
| positive             | 41         | 36          | 1.8 (0.8–4.1) | 0.159 | 0.8–4.1 | <.001 |
| negative             | 117        | NR          |                   |                   |               | .159 |
| Lymph node metastasis|            |             | <.001 | 29.7–58.0 | .276 | 2.2 (0.5–9.3) |
| positive             | 44         | 22          | 120.4–150.7 | 29.7–58.0 | 120.4–150.7 | .001 |
| negative             | 136        | NR          | 27.7–71.7 | 27.7–71.7 | 27.7–71.7 | .001 |
| Histological grade   |            |             | .031 | 92.4–109.8 | .276 | 2.2 (0.5–9.3) |
| GT and G2            | 101        | NR          | 37.9–62.3 | 97.5–114.3 | 37.9–62.3 | .001 |
| G3                   | 50         | 21          | 97.5–114.3 | 97.5–114.3 | 97.5–114.3 | .001 |
| TMN stage            |            |             | .276 | 27.7–71.7 | .276 | 2.2 (0.5–9.3) |
| I and II             | 106        | NR          | 27.7–71.7 | 97.5–114.3 | 97.5–114.3 | .001 |
| III and IV           | 60         | 36          | 37.9–62.3 | 37.9–62.3 | 37.9–62.3 | .001 |

P = P value, NR = not reached, GIT = gastrointestinal tract, HR = Hazard ratio, CI = confidence interval.
incidence of GEP-NEN differed widely among countries. Nevertheless, the rising trend in incidence was observed in studies from the United States, Norway and Taiwan,[2,4,5] which has aroused research attention worldwide. However, it is controversial whether this increase is due to the improvement in diagnostic techniques or the increased attention of doctors. GEP-NENs are classified as functional and nonfunctional tumor according to symptoms associated with hormone over-
production or not. Guo et al summarized the literature published from 1954 to 2011 in China, and found that 89.6% of GEP-NENs were functional.[6] However, in our cohort, functional tumors only accounted for 3.9%, including four insulinomas and 2 ACTH-secreting tumors that all occurred in the pancreas, while nonfunctional tumors with nonspecific symptoms comprised most GEP-NENs. Pancreatic and rectal NENs accounted for almost two thirds of all cases, which might be attributed to the widespread use of abdominal imaging and digestive endoscopy during workup for nonspecific symptoms, or detected accidentally in a regular check-up on the early stage before disease progression. Carcinoid syndrome is a specific manifestation of NEN, which included a series of complicated features like episodic flushing, abdominal pain, diarrhea, asthma and tachycardia, and it occurs in ~18% of jejunioileal NENs.[1,7] None of our cases presented with carcinoid syndrome, which might have been related to the small number of jejunioileal NENs in our cohort, or unawareness of the information collectors in early history-taking and physical examination.

It has been confirmed that GEP-NEN presents its heterogeneity in relation to the diversity of its tissue origin. Many researches have shown significant disparity in the distribution of tumor primary sites, and the small intestine and rectum were the most frequent in the United States, Austria and Norway.[12,5,6] Instead, the commonest primary sites were the pancreas and rectum in Japan, Hong Kong and China.[6,5,10] which is consistent with our study. We assumed that that discrepancy maybe due to the ethnic and environmental variation in carcinogenesis of GEP-NEN. Still, it is necessary to explore further on the carcinogenesis of GEP-NEN and increase the number of patients in epidemiological study.

In our cohort, tumor grade and TNM stage were determined according to the latest revised classification,[4,5] which facilitated comparison of clinicopathological characteristics, prognostic features and clinical outcome of GEP-NEN. In terms of grading in our series, G1 tumors accounted for 49.7% of all cases, followed by G3 (33.6%) and G2 (16.8%), which was similar to previous research.[11,12] whereas the proportion of patient declined as the grade advanced in other studies.[13-15] Taking patients' medical history into consideration, the higher proportion of G1 tumors was probably the consequence of indolent nature of tumor and increased routine health examinations, while G3 tumor had higher malignancy, thus progressed faster and its clinical manifestations appeared earlier than other grades. Patients with lymph node and distant metastasis at initial diagnosis accounted for 27.1% and 9.7%, respectively, while the distant metastasis rate increased to 25.8% during follow-up. In accordance with several other studies, the liver was the predominant location of distant metastasis.[9,12]

In our research, surgical resection was the major treatment as it is the only potential cure for GEP-NEN at present.[16,17] Palliative surgery was used in advanced cancer for cytoreduction and relief of obstruction to gain better quality of life. Except for surgical resection, chemotherapy, interventional therapy like TACE, biological therapy and targeted therapy were common alternatives for patients with GEP-NEN under different circumstances. Chemotherapy was usually applied to poorly differentiated and high-stage tumors. First-line systemic chemotherapy with a platinum-based agent (cisplatin or carboplatin) and etoposide is recommended for most patients with advanced GEP-NEN.[18] Two of the most commonly used chemotherapeutic regimens in our study were etoposide-platinum and irinotecan-platinum combinations. Different combinations of other chemotherapeutic drugs like capecitabine, temozolomide, streptozotocin, and 5-fluorouracil were also frequently used to treat GEP-NEN.[19] TACE is an appropriate and reliable interventional therapy that is usually used to treat liver metastasis. Also, biological therapy is a crucial treatment in functional GEP-NEN to control hormone-related symptoms. Clinically, somatostatin analogues such as octreotide and lanreotide are now frequently administered to suppress excess hormone secretion.[20] Furthermore, targeted drugs like sunitinib and everolimus have already went through a randomized, double-blind, prospective and placebo-controlled phase III trial.[21,22] which can significantly extend progression-free survival.

The prognosis of GEP-NEN is more favorable than that of carcinoma. The estimated overall 5-year survival rate of our study was 51.0%, which was similar to that in Taiwan, Surveillance Epidemiology and End Results and NRC registry.[4,5,15] Nevertheless, studies in the UK, Australia and Spain had higher survival rates.[8,23,24] This regional discrepancy might be explained by ethnic origin, different primary tumor origin, and diverse treatment strategies applied to patients. We demonstrated that incidental diagnosis, maximum tumor diameter and tumor stage, lymph node and distant metastasis, TNM stage and histological grade were significant prognostic factors of survival in patients with GEP-NEN, which partly concurred with some large retrospective cohort studies in Hong Kong, Guang Zhou, and Germany.[10,11,25] Nonetheless, histological grade was the only independent prognostic factor for long-term survival according to Cox-proportional hazard model analysis. This disparity was probably due to different data processing methods and small sample size, which may have led to statistical bias.

Recently, there have been some advancement in the molecular typing of NEN. A whole-genome sequencing has revealed distinctive copy-number variation and single-nucleotide variant patterns and reclassified insulinomas and nonfunctional pancreatic NEN into 5 molecular subtypes.[26] This study explained the correlation between clinical typing and molecular typing, proposed new prognostic indicators, and provided a research basis for clinical precision therapy. Another study reported that molecular subtype (RB1 mutation and the RB1 wild-type) of pulmonary large-cell neuroendocrine carcinoma could predict chemotherapy treatment outcome, the patients with RB1 wild-type large-cell neuroendocrine carcinoma treated with chemotherapy had a significantly longer overall survival.[27] Moreover, a research about small intestinal NEN classified it into 3 groups based on molecular profiling, which are associated with significant difference in progression-free survival after surgical resection. Those studies indicated that the novel molecular classifications of NEN could provide new insight into the clinical management of NEN patients, but more investigation of both clinical and basic research are needed.[28]
either the United States or the UK,\textsuperscript{[11,13,24]} thus there is an urgent need to explore the molecular mechanisms and combine them with large clinical studies, to establish a more effective treatment and reliable method for early detection of GEP-NEN. In addition, with large clinical studies, to establish a more effective treatment need to explore the molecular mechanisms and combine them.

**Author contributions**

Hua Liu, Rongli Xie, Zhiwei Xu and Jian Fei conceived the idea; Hua Liu, Rongli Xie, Zhiwei Xu, Min Ding, Dan Tan, Jun Zhang, and Dongjie Shen conducted the analyses; all authors contributed to the writing and revisions.

**References**

1. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008;9:61–72.

2. Yao JC, Hassan M, Phan A, et al. One hundred years after “carcinoid”: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063–72.

3. Modlin IM, Lye KD, Kidd M. A 3-decade analysis of 13,715 carcinoid tumors. Cancer 2003;97:934–59.

4. Tsai H-J, Wu C-C, Tsai C-R, et al. The epidemiology of neuroendocrine tumors in Taiwan: a nation-wide cancer registry-based study. PLoS One 2013;8:e62487.

5. Hanso O, Gustafsson BI, Kidd M, et al. Neuroendocrine tumor epidemiology: contrasting Norway and North America. Cancer 2008;113:2653–64.

6. Ljung G, Chengwei T. Current status of clinical research on gastroenteropancreatic neuroendocrine tumors in China. (In Chinese). Chin J Gastroenterol 2017;17:276–8.

7. Massironi S, Sciola V, Peracchi M, et al. Neuroendocrine tumors of the gastro-entero-pancreatic system. World J Gastroenterol 2008;14:5377–84.

8. Malik I, Chua YJ, Butt NS, et al. Single institutional series of neuroendocrine tumors managed in the Australian Capital Territory. Asia Pac J Clin Oncol 2016;12:e133–40.

9. Chan DT, Luk AY, So WY, et al. Natural history and outcome in Chinese patients with gastroenteropancreatic neuroendocrine tumours: a 17-year retrospective analysis. BMC Endocr Disord BioMed Central 2016;16:12–9.

10. Ito T, Sasano H, Tanaka M, et al. Epidemiological study of gastroenteropancreatic neuroendocrine tumours in Japan. J Gastroenterol 2010;45:234–43.

11. Jiao X, Li Y, Wang H, et al. Clinicopathological features and survival analysis of gastroenteropancreatic neuroendocrine neoplasms: a retrospective study in a single center of China. Chin J Cancer Res 2015;27:258–66.

12. Wang Y-H, Lin Y, Xue L, et al. Relationship between clinical characteristics and survival of gastroenteropancreatic neuroendocrine neoplasms: a single-institution analysis (1995–2012) in South China. BMC Endocr Disord 2012;12:30.

13. Cho JH, Ryu JK, Song SY, et al. Prognostic validity of the American Joint Committee on cancer and the European Neuroendocrine Tumors Staging Classifications for Pancreatic Neuroendocrine Tumors: a retrospective nationwide multicenter study in South Korea. Pancreas 2016;45:941–6.

14. Massironi S, Rossi RE, Casazza G, et al. Chromogranin A in diagnosing and monitoring patients with gastroenteropancreatic neuroendocrine neoplasms: a large series from a single institution. Neuroendocrinology 2014;100:240–9.

15. Ye BX, Heng D, Jiang LQ, et al. Application of AJCC/UICC and WHO-2010 classifications for GEP-NEN in Chinese patients. J Dig Dis 2015;16:264–71.

16. Janson ET, Sorbye H, Welin S, et al. Nordic Guidelines 2010 for diagnosis and treatment of gastroenteropancreatic neuroendocrine tumours. Acta Oncol. 2010;49:740–56.

17. Kulke MH, Siu LL, Teppera JE, et al. Future directions in the treatment of neuroendocrine tumors: consensus report of the National Cancer Institute Neuroendocrine Tumor clinical trials planning meeting. J Clin Oncol. 2011;29:934–43.

18. Strosberg JR, Coppola D, Klimstra DS, et al. The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas. Pancreas. 2010;39:799–800.

19. Alexandraki KI, Karapanagioti A, Karoumpalis I, et al. Advances and current concepts in the medical management of gastroenteropancreatic neuroendocrine neoplasms. Biomed Res Int 2017;2017:9856140–212.

20. Oberg K, Lamberts SWJ. Somatostatin analogues in acromegaly and gastroenteropancreatic neuroendocrine tumours: past, present and future. Endocr Relat Cancer 2016;23:R51–66.

21. Raymond E, Dahan L, Raoul J-L, et al. Sunsitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011;364:501–13.

22. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364:514–23.

23. Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, et al. Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). Ann Oncol 2010;21:1794–803.

24. Legue C, Rachet B, Coleman MP. Survival from malignant digestive endocrine tumors in England and Wales: a population-based study. Gastroenterology 2007;132:899–904.

25. Pape U-F, Berndt U, Müller-Nordhorn J, et al. Prognostic factors of long-term outcome in gastroenteropancreatic neuroendocrine tumours. Endocr Relat Cancer 2008;15:1083–97.

26. Hong X, Qiao S, Li F, et al. Whole-genome sequencing reveals distinct genetic bases for insulinomas and non-functional pancreatic neuroendocrine tumours: leading to a new classification system. Gut 2020;69:877–87.

27. Derks JL, Leblay N, Thunnissen E, et al. Molecular subtypes of pulmonary large-cell neuroendocrine carcinoma predict chemotherapy treatment outcome. Clin Cancer Res 2018;24:33–42.