Clinical features and outcomes of gastric neuroendocrine tumors after endoscopic diagnosis and treatment

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Chen-Shuan Chung, MD, MSC,∗ Y-Y Chu, MD,∗, Cho-Lun Tsai, MD,∗∗, Wei-Chih Sun, MD,∗∗∗, Hsiu-Po Wang, MD,∗∗∗∗, Kuan-Chih Chen, MD,∗∗∗∗, Jung-Chun Lin, MD, PhD,∗∗∗∗, Bao-Chung Chen, MD,∗∗∗∗, Wei-Chih Sun, MD, PhD,∗∗∗∗, Hsu-Heng Yen, MD,∗∗∗∗, Chiung-Yu Chen, MD,∗∗∗∗, I-Chen Wu, MD, PhD,∗∗∗∗, Chaohung Kuo, MD, PhD,∗∗∗∗, Hisang-Yao Shih, MD,∗∗∗∗, Ming-Jong Bair, MD,∗∗∗∗, Jack P. Wang, MD,∗∗∗∗, Wen-Hao Hu, MD,∗∗∗∗, Chang-Shyue Yang, MD,∗∗∗∗, Ming-Luen Han, MD,∗∗∗∗, Tsu-Yao Cheng, MD, PhD,∗∗∗∗, Chao-Ming Tseng, MD,∗∗∗∗, Ming-Chang Tsai, MD,∗∗∗∗, Ming-Luen Hu, MD,∗∗∗∗, Hsiu-Po Wang, MD,∗∗∗∗

Abstract

Gastric neuroendocrine tumors (GNETs) are a heterogeneous group of neoplasm with varying biological characteristics. This study aimed to investigate the clinical features and outcomes of GNET patients after endoscopic diagnosis and treatment in a multicenter registry. Patients with GNETs confirmed histologically were recruited from 17 hospitals between January 2010 and April 2016 in Taiwan. Clinical, laboratory, radiological, endoscopic, pathological data, treatment strategies, follow-up periods, and survivals were collected retrospectively. Totally 187 (107 female, 80 male) patients were recruited. Mean (± standard deviation [SD]) age and size of tumors were 63.2-year-old (± 14.6) and 2.3-cm (± 3.0). World Health Organization (WHO) grading were 93 (49.7%) G1, 26 (13.9%) G2, 40 (21.4%) G3, and 28 (15.0%) unknown. G3 patients were older (mean ± SD) 71.6 ± 12.4 vs. 60.9 ± 14.3 ± 15.4 years, larger (6.1 ± 4.0 vs. 1.2 ± 1.3/2.4 ± 2.5 cm), more distally located (35.0% vs. 7.6%/15.4%), lower proportion of superficial lesions (17.5% vs. 61.9%/53.8%) and higher rates of lymphovascular invasion (32.5% vs. 3.2%/7.7%) than G1/G2. There was no nodal or organ metastases despite different grading of lesions<10mm and those <20mm limited to mucosa and submucosa layers. GNETs larger than 20mm with G1, G2, and G3 had lymph node (LN) metastatic rates of 21.4%, 30.0%, and 59.3%, respectively. Differences were different between grading for those >20mm (log-rank test \( P < .02 \)). Male gender (\( P = .01 \)), deeper invasion (\( P = .0001 \)), nodal (\( P < .0001 \)), and distant organ metastases (\( P = .0001 \)) were associated with worse outcome. In conclusion, treatment...
strategies for GNET should be decided by grading, size, invasiveness, and LN metastasis risk. Curative endoscopic resection is feasible for G1/2 lesions less than 20 mm and limited to mucosa/submucosa layers without lymphovascular invasion.

**Abbreviations:** ECL = enterochromaffin-like, EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection, GEP-NET = gastroenteropancreatic neuroendocrine tumor, GI = gastrointestinal, GNET = gastric neuroendocrine tumor, LN = lymph node, MEN = multiple endocrine neoplasia, NCCN = National Comprehensive Cancer Network, NET = neuroendocrine tumor, SD = standard deviation, WHO = World Health Organization, ZES = Zollinger–Ellison syndrome.

**Keywords:** carcinoid tumor, endoscopic resection, multicenter study, neuroendocrine tumor, stomach

**1. Introduction**

In the early twentieth century, neuroendocrine tumors (NETs), which arise from cells of diffuse neuroendocrine system in many organs of human body, have been noted to behave differently as compared to carcinoma by Oberndorfer with the first description of a “karzinoid.”[11] Due to improvements in diagnostic technology, including endoscopy, radiological modalities, and an increased awareness, the incidence of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) has increased gradually. Over the past 4 decades, the age-adjusted incidence of GEP-NETs has increased steadily with approximately 3 to 5-fold change in western countries, especially for gastrointestinal (GI) NETs with the greatest increase in rectal and gastric neuroendocrine tumors (GNETs) patients.[2,3] The ratio of GNET to all GI-NETs, ranging from 11.9% to 23% among different countries, has increased nearly 10-fold in the USA, and 23-fold in men and 47-fold in women in the USA.[2,3] In Taiwan, the analysis of nationwide cancer registry database revealed that the stomach was ranked the third most common site among newly-diagnosed NETs of the whole body.[4] Moreover, GNETs are among the top 5 prevalent histology of gastric polyoid lesions.[5,6] Nowadays, more and more GNETs are being diagnosed incidentally by endoscopy in the absence of clinical symptoms. Therefore, to understand the clinical manifestation and management of this emerging disease is very important.

GNETs are classified into 3 subgroups with differences in clinical manifestations and prognosis.[7–9] Type I and II GNETs are often female preponderant, multiple, small size (<10–20 mm), proximal located, well-differentiated [World Health Organization (WHO) grade (G) 1 and 2], limited to mucosa/submucosa layers without lymphovascular invasion. Strategies for GNET should be decided by grading, size, invasiveness, and LN metastasis risk. Curative endoscopic resection is feasible for G1/2 lesions less than 20 mm and limited to mucosa/submucosa layers without lymphovascular invasion.

**2. Materials and methods**

Between January 2010 and April 2016, patients with diagnosis of GNETs confirmed histologically were recruited from 17 hospitals in Taiwan. Data were collected retrospectively by doctors who filled out the uniform case record files. WHO 2010 classification system was used for grading of differentiation.[13] Clinical classification was based on the following criteria: type I GNETs were those with (i) no evidence of MEN-ZES; and (ii) positive anti-parietal cell antibodies; or (iii) presence of ECL cell hyperplasia or gastric atrophy based on endoscopy or histology, or (iv) evidence of hypergastrinemia (>450pg/mL) in the case of no evidence of autoantibodies or hyperplasia of ECL cells; type II GNETs were those with presence of type I multiple endocrine neoplasia (MEN-I) or ZES; and type III were patients not fulfilling criteria for type I and II.

Clinical, laboratory, radiological and endoscopic data were collected at the time of initial diagnosis of GNETs at each institution. All the pathologists in each study institution used WHO 2010 criteria for NET diagnosis. Data analyzed included demographic characters, tumor size, location and number, depth of tumor invasion, lymphovascular invasion, tumor stages, management approach, and presence of_H. pylori_infection (histology or rapid urease test), serum gastrin level, follow-up periods and survivals. The depth of tumor invasion was recorded by using resected specimens for histology or endoscopic ultrasonography. Radiological examinations included computed tomography or magnetic resonance imaging to evaluate nodal or distant organ metastases. Each participating institution approved this retrospective multicenter study by the ethics committee and informed consent from individual patients was not required because of observational study design.

**2.1. Statistical analysis**

Continuous data were expressed as means or medians [± SD and ranges] as appropriate, and category data were expressed as number (percentage). The overall survival of patients was plotted in Kaplan–Meier survival plots. Univariate and multivariate analyses were performed to evaluate the risk factor for disease-related mortality. All statistical analyses were accomplished using Stata software, version 12.0 (StataCorp LP, College Station, TX).

**3. Results**

Demographic data of patients are shown in Table 1. Totally 187 GNET patients were recruited from 17 hospitals. There were 107 female (57.2%) and 80 male patients (42.8%). The mean (± SD, range) age and size were 63.2-year-old (± 14.6, 21–95) and 2.4-
The rate of clear resection margin according to different management approaches are shown in Table 3. Among GNETs≤10mm, removal of tumors by piecemeal biopsy, polypectomy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD) achieved histological resection margin free rates of 45.5%, 45.5%, 68.8%, and 75%, respectively for G1, and 33.0%, 50.0%, 100%, and 100%, respectively for G2 tumors. For G1 tumors with size between approximately 11 and 20mm, the resection margin free rates were 0%, 100%, and 100% for polypectomy, EMR, and ESD, respectively. Univariate and multivariate analyses of risk factors for disease-related mortality were shown in Table 4. In the univariate analysis, male sex (P < .025), greater size, more advanced grading/staging, presence of lymphovascular invasion, and distant metastasis (all with P < .001) were associated with higher mortality risk. In the multivariate analysis, more advanced stage (P = .034) was the independent risk factor for disease-related mortality. Supplementary Table 2, http://links.lww.com/MD/C465 and Figures 1 and 2 revealed the survival of GNETs with different grading and size. Survival rates were best in G1 and worst in G3 lesions (log-rank test P < .001). Patients with tumor larger than 20mm had worse outcome. Among GNETs larger than 20mm, overall mortality rates for G1, G2, and G3 lesions were 28.6%, 11.1%, and 55.6%, respectively, whereas disease-related mortality rates were 21.4%, 0%, and 44.4%, respectively. Survival rates were not different between lesions less than 20mm (log-rank test P = .94 for lesions ≤10mm, and P = .65 for those between 11~20mm) with different grading, but statistically significant difference for those larger than 20mm (log-rank test P = .002). Male gender (log-rank test P = .01), deeper invasion

| Table 1 | Demographic data of enrolled patients by WHO grading. |
|---------|------------------------------------------------------|
| Total (No = 187) | G1 (No = 93) | G2 (No = 26) | G3 (No = 40) | P-value (G3 vs. G1/G2) |
| Men/Women (%) | 80/107 (42.8/57.2) | 29/64 (32.5/67.5) | 13/9/18 (32.5/22.5/45.0) | .0001 / .0022 |
| Mean age (±SD, range), years | 63.2 (±14.6, 21~89) | 60.9 (±14.3) | 71.6 (±12.4) | .002 / .0001 |
| Surviving multiple (% | 37/119 (19.6/54.5) | 30/64 (28.1/61.9) | 24/52 (53.8/46.2) | .0012 / .0001 |
| Mean size (±SD, cm) | 2.4 (±0.3, 1.0~1.5) | 1.2 (±1.3) | 2.4 (±0.2) | .0001 / .0002 |
| Mean follow-up period (±SD, range), years | 2.5 (±2.6, 0.1~1.1) | 2.4 (±2.5) | 2.7 (±1.8) | .0001 / .0002 |
| Location (antrum/body/fundus | 32/107/50 (16.7/53.5/29.8) | 76/67/11 (51.5/48.5/0) | 11/17/11 (10.0/77.8/22.2) | .0001 / .0002 |
| Radius/radial/ranulum (mm) | (17.5/7.5/3.5) | (15.8/4.8/1.8) | (35.0/7.5/2.5) | .0001 / .0002 |
| Invasive depth (mm/m/mp/tumor, UK) (%) | 1.6/7.7/5.1 | 2.2/2.7/8 | 3.8/3.3/8/0 | 17.5/5.1/50.0 |
| Lymphovascular invasion (+/−/−/−/−) (%) | (10.0/28.5/50.0/10.0/10.0) | (19.2/24.6/50.0/50.0) | (35.0/50.0/50.0) | .0001 / .0002 |
| Mean gastrin level (±SD, range), pg/mL | 584.8 (±78.6/4.0~1426) | 792.3 (±202.0) | 900 (NA) | .0001 / .0002 |

NA = not applicable, UK = unknown data, WHO = World Health Organization.

| Table 2 | Status of nodal and distant organ metastasis. |
|---------|-----------------------------------------------|
| Lymphovascular invasion (%) | Lymph node metastasis (%) | Distant metastasis (%) |
| ≤10mm | G1 (No=59) | 0 (0) | 0 (0) | 0 (0) |
| | G2 (No=10) | 0 (0) | 0 (0) | 0 (0) |
| | G3 (No=1) | 0 (0) | 0 (0) | 0 (0) |
| 11~20mm | G1 (No=13) | 1 (7.7) | 1 (7.7) | 0 (0) |
| | G2 (No=6) | 1 (16.7) | 1 (16.7) | 0 (0) |
| | G3 (No=3) | 0 (0) | 0 (0) | 0 (0) |
| >20mm | G1 (No=14) | 3 (21.4) | 3 (21.4) | 2 (14.3) |
| | G2 (No=10) | 2 (20.0) | 3 (30.0) | 5 (50.0) |
| | G3 (No=27) | 12 (44.4) | 16 (59.3) | 18 (66.7) |

The majority were multiple in number (75.4%) and proximal located (71.1%) at the corpus, fundus or cardia of stomach. The invasive depth of most GNETs was mucosa (28.9%) and submucosa (20.9%) layers and 67.4% did not have lymphovascular invasion on histology. Grading of these lesions were 93 (49.7%) G1, 26 (13.9%) G2, 40 (21.4%) G3, and 28 (15.0%) unknown grading lesions. GNET patients with G3 were more males (72.5% vs. 31.2%/30.8%, P = .0001/.0022), older (mean ± SD, 71.6 ± 12.4 vs. 60.9 ± 14.3/56.7 ± 15.4 years, P = .0002/0001) and larger (6.1 ± 4.0 vs. 1.2 ± 1.3/2.4 ± 2.5 cm, P = .0001/0002) than G1/G2 patients. More G3 lesions were located at antrum than G1/G2 lesions (35.0% vs. 7.6%/15.4%, P = .003/04). Proportion of lesions limited to mucosa and submucosa layers in G1/G2 lesions were higher than G3 tumors (61.9%/53.8% vs. 17.5%, P = .0003/0012), G3 GNETs presented more lymphovascular invasion than G1/G2 lesions (32.5% vs. 3.2%/7.7%, P ≤ .0001/0057). The mean gastrin level for G1, G2, and G3 lesions were 792.3, 1000 and 40.4 pg/mL, respectively.

Demographic data of patients with different clinical classifications are shown in Supplementary Table 1, http://links.lww.com/MD/C463. Type I GNET was the most common 1 (142/187 = 75.9%), followed by type III (44/187 = 23.5%) and type II (1 patient) tumors in this study. More female patients were noted in type II/III (64.8%/100% vs. 31.8%, P = .0002/NA) than in type I GNETs. There were no tumors with G3 in type I and II GNETs, but 90.9% of type III GNETs were grading G3. Higher proportion of type III GNETs were distally-located (37.5% vs. 12.0%/0% at antrum, P = .032/NA), deeper invasion (35.0% vs. 4.9%/0% beyond serosa, P = .003/NA), and lymph node (LN) metastasized (45.5% vs. 7.7%/0%, P = .0002/NA) than type III. The H pylori positive rates in type I, II and III GNETs were 35.9%, 0%, and 9.1%, respectively.

Table 2 discloses the metastatic rates of LN and distant organ. In GNETs less than 10 mm, there was no patient with nodal or distant organ metastasis despite different grading. Among tumors with a size between approximately 11 and 20 mm, there was 1 (7.7%) G1 patient presenting lymphovascular invasion and LN metastasis with invasion of muscularis propria. There were 4 G2 lesions with size between approximately 11 and 20 mm and all of them underwent surgery. One involving mucosa (stage I), 1 invading submucosa (stage IIA) and 2 with invasion to muscularis propria (stage IIA and IIIb) were found. Among 2 G2 patients with involvement of muscularis propria, 1 (50%) had LN metastasis. GNET patients with tumors larger than 20 mm with G1, G2, and G3 had LN and distant organ metastatic rates of 21.4% and 14.3%, 30.0% and 50.0%, and 59.3% and 66.7%, respectively.
Table 3
Resection margin free rates by different endoscopic resection and surgical management.

| Endoscopic management (%) | G1 | G2 | G3 | G1 | G2 | G3 | G1 | G2 | G3 |
|---------------------------|----|----|----|----|----|----|----|----|----|
| Biopsy                    | 5/11 (45.5%) | 1/3 (33.3%) | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| Polypectomy               | 5/11 (45.5%) | 1/2 (50.0%) | 0/0 | 0/1 (0.0%) | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| EMR                       | 11/16 (68.8%) | 1/1 (100.0%) | 0/0 | 2/2 (100.0%) | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| ESD                       | 3/4 (75.0%) | 3/3 (100.0%) | 0/0 | 3/3 (100.0%) | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| Surgical resection        | 8/8 (100.0%) | 1/1 (100.0%) | 1/1 (100.0%) | 4/4 (100.0%) | 4/4 (100.0%) | 2/2 (100.0%) | 13/13 (100.0%) | 8/8 (100.0%) | 14/14 (100.0%) |

EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection.

Table 4
Univariate and multivariate analyses to evaluate risk factors for disease-related mortality.

| Univariate analysis | Multivariate analysis |
|---------------------|-----------------------|
| OR                  | 95% CI                | P-value | OR                  | 95% CI                | P-value |
| Age (every 1-year older) | 1.03 | 0.99–1.07 | .071 | 1.00 | 0.92–1.08 | .914 |
| Male sex            | 3.00 | 1.15–7.83 | .025 | 0.99 | 0.09–11.09 | .991 |
| Size (every 10 mm increment) | 1.37 | 1.19–1.58 | <.001 | 0.70 | 0.40–1.21 | .206 |
| Grade               | 3.13 | 1.81–5.43 | <.001 | 1.38 | 0.40–4.75 | .604 |
| Lymphovascular invasion | 10.37 | 2.80–38.42 | <.001 | 10.51 | 0.62–179.52 | .104 |
| Distant metastasis  | 9.21 | 3.40–24.92 | <.001 | 0.19 | 0.01–2.83 | .231 |
| Stage               | 2.09 | 1.54–2.84 | <.001 | 2.36 | 1.07–5.20 | .034 |

CI = confidence interval, OR = odds ratio.

Figure 1. Comparison of survivals according to different grading and size. A)-overall, B) ≤1 cm, C) >1 cm and ≤2 cm, D) >2 cm.
4. Discussion

In this retrospective multicenter study conducted in Taiwan, we characterized the clinical course, management approaches and outcomes of GNETs. The majority of GNETs belong to G1 and clinical classification type I, which are associated with female predominance, smaller size, proximal location in stomach and relatively optimal outcomes. GNETs with G3 or type III were predominantly male, larger size, possibly with distal location, and poor prognosis. Endoscopic resection, including modified EMR or ESD, could be used for curative treatment of GNETs less than 10 mm despite of grading and G1/G2 tumors with size between approximately 11 and 20 mm without lymphovascular invasion and limited to mucosa and submucosa layers. Tumors with G3 larger than 20 mm had the worst survival and aggressive treatment should be considered. Male gender, deep invasiveness, nodal, and distant organ metastases were associated with worse prognosis.

With the widespread use of endoscopy examination for many GI diseases, more and more GNETs, which have been deemed as rare disease, are being detected. According to studies from large number of national histopathology or endoscopy database, about 3.3% of polypoid lesions in stomach belonged to NETs with prevalence about 0.06% in general population.[5,6] It is sometimes difficult to be differentiated from non-neoplastic gastric polyps, although some typical magnifying endoscopic features under narrow-band imaging system could be found (central depression with absent pits, and dilated darkish-brown subepithelial vessels with cork-screw capillaries) (Fig. 3). Additionally, GNETs are more associated with younger age, female and gastric atrophy than other histology types of gastric polypoid lesions.[5,6,15] Another report from nationwide cancer registry also found that the proportion of GNETs among all gastric malignancies and GI tract NETs has increased from 0.3% to 1.77% and from 2.4% to 8.7%, respectively.[15] Among epidemiological data from different countries, the ratio of GNET to all GI tract NET range from approximately 11.9% to 23%.[2,3,10] In Taiwan, the cancer registry data showed that the stomach is the third (7.4%) most common primary site of NET among other organs of human body. Therefore, facing this emerging disease entity, our nationwide multicenter study is of significance to provide information about the clinical manifestations, management approaches and outcomes for GNETs in Taiwan.

GNETs can be categorized into well and poorly differentiated tumors and subdivided into those arising from ECL cell hyperplasia secondary to excess gastrin stimulation (types I and II, primarily well-differentiated) and sporadic tumors (type III, well or poorly differentiated).[11,16] Some studies advocate the subdivision of type III GNETs into 2 groups (type III and IV) which both are gastrin-independent non-ECL cell origin, where type III tumors are sporadic nonfunctioning and type IV tumors are poorly differentiated or arise from adrenocorticotropic
hormone, serotonin-cells or are of mixed endocrine-exocrine etiology.\[1,2]\ However, to subdivide type III into 2 subtypes is of little clinical relevance, since the outcomes are poor and the managements are similar for both type III and IV GNETs. Type I tumors account for approximately 70% to 80% of GNETs and might be associated with H pylori related gastritis, chronic atrophic gastritis, autoimmune gastritis, and pernicious anemia.\[10-12,16]\ More females are found in type I GNETs in most studies, including ours (Supplementary Table 1, http://links.lww.com/MD/C465, female 64.8%), but 1 Asian multicenter study conducted in Japan showed a male preponderance (male 53.7%).\[14\] Usually, type I GENTs are multiple with proximal location in stomach and associated with H pylori infection.\[11,12,16]\ But from Asian data, a Japanese retrospective multicenter study showed higher proportion (53.7%) of solitary in type I GNETs, which was similar to our study (72.5%), whereas higher positive rate for H pylori infection in type I GNETs than other types (Japanese study 24.4%, ours 35.9%).\[14\] It seems that the epidemiologic data vary between different countries and to understand the difference in clinical manifestation in different areas is very crucial. In our study (Supplementary Table 1, http://links.lww.com/MD/C465), we also found that type III GNETs were more commonly male, older, larger size, more often distal location in stomach, with deeper invasion of the gastric wall, and higher risk of nodal metastasis than type I and II tumors. There was only 1 type II case with MEN-I in our study. This young female patient with type II GNET had multiple polypoid tumors with size less than 10 mm at the whole stomach with grading G1, invasion of submucosa but without metastasis. Her serum gastrin level was 986 pg/mL and she received multiple sessions of polypectomy combining somatostatin analogue therapy with stable disease. Therefore, type I and II GNETs have better outcomes than type III tumors.

NETs are considered to be slow-growing and lower malignant potential than traditional carcinomas.\[1,15]\ Thus, conservative management strategies rather than surgical intervention are to be preferred. Previously, the European Neuroendocrine Tumor Society (ENETS) and National Comprehensive Cancer Network (NCCN) guidelines recommended simple surveillance for lesions less than 10 mm limited to mucosa and submucosa layers.\[18,19]\ For locoregional lesions between approximately 10 and 20 mm with hypergastrinemia, and grading in our study are shown in Table 2. There was no patient with a tumor size between approximately 11 and 20 mm, the LN metastatic rates were closely associated with the depth of invasion. There was 1 (7.7%) G1 patient and 1 (25.0%) G2 patient with a tumor size between approximately 11 and 20 mm had LN metastasis, with invasion of muscularis propria. For those larger than 20 mm, the LN and distant organ metastatic rates increased in proportion of the severity of grading. Therefore, we recommend that endoscopic resection be used for curative treatment of GNETs less than 10 mm despite of grading and G1/G2 tumors with size between approximately 11 and 20 mm on the premise that lymphovascular invasion is not found in resected specimen and invasion is confined to mucosa and submucosa layers.

There are some limitations in this study. First, there are many missing data and the diagnostic workup and management approach, especially endoscopic resection methods, were not standardized because of retrospective study design. Some diminutive lesions were endoscopically biopsied without suspicion of histopathologic diagnosis of NET and some of those without R0 could not be identified at surveillance endoscopy. Second, all the pathologic data was based on medical records review and there was no centralized pathologic review of each specimen. However, pathologists in each study hospital used WHO 2010 criteria for NET diagnosis. Finally, the case number is small despite multicenter enrollment, especially when there was only 1 case classified as type II GNET. Moreover, the follow-up period was short and long-term outcome could not be revealed by this study.
In conclusion, this study was the first multicenter study in Taiwan to evaluate the clinical manifestations, management approaches and outcomes of GNET. We proposed a standardized work-up and treatment recommendations, which is illustrated in Figure 4. Further prospective analysis of a cohort with standardized diagnostic and management protocols are warranted to further our understandings of GNETs.

Author contributions

Conceptualization: Chen-Shuan Chung, Cho-Lun Tsai, Yin-Yi Chu, Kuan-Chih Chen, Jung-Chun Lin, Chiung-Yu Chen, Hsiu-Po Wang.

Data curation: Chen-Shuan Chung, Cho-Lun Tsai, Yin-Yi Chu, Kuan-Chih Chen, Jung-Chun Lin, Bao-Chung Chen, Wei-Chih Sun, Hsu-Heng Yen, Chiung-Yu Chen, I-Chen Wu, Chao-Hung Kuo, Ming-Jong Bair, Jack P Wang, Wen-Hao Hu, Chang-Shyue Yang, Ming-Luen Han, Tsu-Yao Cheng, Chao-Ming Tseng, Ming-Chang Tsai, Ming-Luen Hu, Hsiu-Po Wang.

Formal analysis: Chen-Shuan Chung, Yin-Yi Chu, Kuan-Chih Chen, Hsiu-Po Wang.

Methodology: Chen-Shuan Chung.

Resources: Cho-Lun Tsai, Yin-Yi Chu, Kuan-Chih Chen, Jung-Chun Lin, Bao-Chung Chen, Wei-Chih Sun, Hsu-Heng Yen, Chiu-Yu Chen, I-Chen Wu, Chao-Hung Kuo, Hisang-Yao Shih, Ming-Jong Bair, Jack P Wang, Wen-Hao Hu, Chang-Shyue Yang, Ming-Luen Han, Tsu-Yao Cheng, Chao-Ming Tseng, Ming-Chang Tsai, Ming-Luen Hu, Hsiu-Po Wang.

Validation: Chen-Shuan Chung, Cho-Lun Tsai, Yin-Yi Chu, Kuan-Chih Chen, Chiu-Yu Chen, I-Chen Wu, Chao-Hung Kuo, Hisang-Yao Shih, Ming-Jong Bair, Jack P Wang, Wen-Hao Hu, Chang-Shyue Yang, Ming-Luen Han, Tsu-Yao Cheng, Chao-Ming Tseng, Ming-Chang Tsai, Ming-Luen Hu, Hsiu-Po Wang.

Writing – original draft: Chen-Shuan Chung, Hsiu-Po Wang.

Writing – review & editing: Chen-Shuan Chung.

Chen-Shuan Chung orcid: 0000-0001-9224-4958

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