**Name of Journal:** *World Journal of Gastrointestinal Oncology*

**Manuscript NO:** 57893

**Manuscript Type:** ORIGINAL ARTICLE

***Retrospective Study***

**Clinicopathological characteristics and prognosis of 77 cases with type 3 gastric neuroendocrine tumours**

Li YL *et al*. Type 3 gastric neuroendocrine tumours

Yuan-Liang Li, Xu-Dong Qiu, Jie Chen, Yu Zhang, Jie Li, Jian-Ming Xu, Chao Wang, Zhi-Rong Qi, Jie Luo, Huang-Ying Tan

**Yuan-Liang Li, Xu-Dong Qiu,** Beijing University of Chinese Medicine, Beijing 100029, China

**Yuan-Liang Li, Xu-Dong Qiu, Chao Wang, Zhi-Rong Qi, Huang-Ying Tan,** Department of Integrative Oncology, China-Japan Friendship Hospital, Beijing 100029, China

**Jie Chen, Yu Zhang,** Department of Gastroenterology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510000, Guangdong Province, China

**Jie Li,** Department of Gastrointestinal Oncology, Peking University Cancer Hospital and Beijing Cancer Hospital, Beijing 100037, China

**Jian-Ming Xu,** Department of Gastrointestinal Oncology, The Fifth Medical Center, Chinese PLA General Hospital, Beijing 100071, China

**Jie Luo,** Department of Pathology, China-Japan Friendship Hospital, Beijing 100029, China

**Author contributions:** Li YL and Qiu XD contributed equally to this work and should be consider as co-first authors; Li YL and Qiu XD wrote the paper; Li YL and Tan HY designed the research; Qiu XD, Chen J, Zhang Y, Li J, and Xu JM collected the data; Wang C and Qi ZR analysed the data; Luo J reviewed the pathology; Tan HY revised the paper.

**Supported by** National Natural Science Foundation of China, No. 81673763; Foundation of Guangzhou Science and Technology Plan, No. 201804010078.

**Corresponding author: Huang-Ying Tan, MD, PhD, Professor,** Department of Integrative Oncology, China-Japan Friendship Hospital, No. 2 Yinghuadong Street, Beijing 100029, China. tanhuangying@263.net

**Received:** July 11, 2020

**Revised:** September 28, 2020

**Accepted:** October 28, 2020

**Published online:**

**Abstract**

BACKGROUND

For the rarity of type 3 gastric neuroendocrine tumours (g-NETs), their clinicopathological characteristics and prognosis are not well illustrated.

AIM

To describe the clinicopathological features and outcome of type 3 g-NETs in the Chinese population.

METHODS

Based on the 2019 WHO pathological classification, the clinicopathological characteristics and prognosis of patients with type 3 g-NETs in China were retrospectively analysed.

RESULTS

A total of 77 patients (55.8% of females) with type 3 g-NETs were analysed, with a median age of 48 years (range: 28-79 years). The tumours were mainly located in the gastric fundus/body (83.1%) and were mostly solitary (83.1%), with a median size of 1.5 cm (0.8-3.5 cm). Of these, there were 37 G1 tumours (48.1%), 31 G2 (40.3%), and 9 G3 (11.7%). Ten (13.0%) and 24 (31.2%) patients had lymph node and distant metastasis, respectively. In addition, type 3 g-NETs were heterogeneous. Compared with G1 NETs, G2 NETs had a higher lymph node metastasis rate, and G3 NETs had a higher distant metastasis rate. G1 and G2 NETs with stage I/II disease (33/68) received endoscopic treatment, and no tumour recurrence or tumour-related death was observed within a median follow-up time of 36 mo. Grade and distant metastasis were identified to be independent risk factors for prognosis in multivariable analysis.

CONCLUSION

Type 3 g-NETs are obviously heterogeneous, and the updated WHO 2019 pathological classification may be used to effectively evaluate their biological behaviors and prognosis. Also, endoscopic treatment should be considered for small (< 2 cm), low grade, superficial tumours.

**Key Words:** Type 3 gastric neuroendocrine tumours; Clinicopathological characteristics; Endoscopic treatment; Prognosis; Chinese population

Li YL, Qiu XD, Chen J, Zhang Y, Li J, Xu JM, Wang C, Qi ZR, Luo J, Tan HY. Clinicopathological characteristics and prognosis of 77 cases with type 3 gastric neuroendocrine tumours. *World J Gastrointest Oncol* 2020; In press

**Core Tip:** Type 3 gastric neuroendocrine tumours (g-NETs) were heterogeneous based on the 2019 WHO pathological classification. Endoscopic treatment was safe and effective for patients with G1 NETs having tumours under 2 cm, confined to the mucosa or submucosa. The prognosis of type 3 g-NETs was related to stage and grade, which were its independent prognostic factors, and the 2019 WHO pathological classification was effective to predict the biological behaviors and prognosis of type 3 g-NETs.

**INTRODUCTION**

Gastric neuroendocrine neoplasms (g-NENs) are a group of rare tumours with strong heterogeneity originating from neuroendocrine cells. With the development of upper gastrointestinal endoscopy and imaging, an increasing number of patients with g-NENs have been found[1,2]. According to the Surveillance, Epidemiology, and End Results database, the age-adjusted incidence increased 6.4 times from 1973 (1.09/100000) to 2012 (6.98/100000). The digestive system was the most common site of NENs, and the stomach was ranked fourth, followed by the small intestine, rectum, and pancreas[3]. In South Korea, Austria, and Argentina, g-NENs accounted for 14.6%, 23%, and 6.9% of gastrointestinal and pancreatic neuroendocrine tumours, respectively[4-6].

According to differentiation, g-NENs can be divided into well-differentiated gastric neuroendocrine tumours (g-NETs) and poorly differentiated gastric neuroendocrine carcinomas (g-NECs). Well-differentiated g-NETs are classified as types 1 to 3 g-NETs[7-9]. Type 1 g-NETs are associated with autoimmune atrophic gastritis with elevated serum gastrin and gastric acid deficiency, while type 2 g-NETs with hypergastrinemia and high gastric acid secretion are related to gastrinoma or multiple endocrine neoplasia type 1 (MEN-1). Patients with type 3 g-NETs have normal serum gastrin, gastric acid secretion, and no related background disease. Types 1 and 2 g-NETs are generally considered indolent and have a low risk of malignancy, while type 3 g-NETs often show aggressive characteristics, including lymphatic invasion and tumour infiltration beyond the submucosa, and a poor prognosis[10,11]. Given the rarity, there are few related studies on type 3 g-NETs. Also, the World Health organization (WHO) pathological classification of gastroenteropancreatic neuroendocrine neoplasms was updated in 2019 and its role has not been well illustrated. Therefore, we are dedicated to exploring the clinicopathological characteristics and prognostic factors of this disease based on the 2019 WHO grading system.

**MATERIALS AND METHODS**

***Patients***

We retrospectively analysed the clinicopathological features of 77 patients with type 3 g-NETs at four NET centres in China from July 2012 to December 2018 [China-Japan Friendship Hospital (*n* = 51), The First Affiliated Hospital of Sun Yat-sen University (*n* = 17), Peking University Cancer Hospital (*n* = 6), and The Fifth Medical Center, Chinese PLA General Hospital (*n* = 3)]. Patients with type 3 g-NETs met the inclusion criteria: (1) Histologically proven well-differentiated g-NETs; (2) normal serum gastrin; and (3) no evidence of types 1 and 2 g-NETs. All pathological results were reviewed by an experienced pathologist. The study obtained the patients’ informed consent and was approved by the clinical research ethics committee of the China-Japan Friendship Hospital.

Endoscopy was used to find the lesion on the stomach and get biopsy, and endoscopic ultrasound (EUS) was performed to assess the infiltration of the gastric wall only when tumour size was larger than 1 cm. Computed tomography and magnetic resonance imaging were used to assess the condition of gastric lesions, the relationship between lesion and adjacent organs or tissues, the status of regional lymph nodes, and distant metastasis. Some patients may undergo somatostatin receptor scintigraphy or 68Ga DATATATE positron emission tomography/computed tomography to assess the status of lymph node and distant metastases.

***Pathological classification and tumor node metastasis staging***

The 5th edition WHO classification (2019) of gastroenteropancreatic neuroendocrine neoplasms was used to determine the pathological grade[9], which is divided into G1 (Ki67 index < 3% or mitoses/2 mm2 < 2), G2 (3% ≤ Ki67 index ≤ 20% or 2 ≤ mitoses/2 mm2 ≤ 20), and G3 (Ki67 index > 20% or mitoses/2 mm2 > 20). Tumour staging was performed using the AJCC 8th Edition Gastric Neuroendocrine Tumour Staging[12].

***Follow-up***

Patients were followed by hospitalization, outpatient service, or telephone. The starting point was the time when the patient's histopathology yielded a diagnosis of g-NET. The deadline for follow-up was August 12, 2019. The end point of the follow-up was the time of tumour-specific death.

***Statistical analysis***

Categorical variables are reported as frequencies or percentages and continuous variables are expressed as medians (interquartile ranges). Comparisons between groups were performed using the Mann-Whitney *U* test or Kruskal-Wallis test. The Kaplan-Meier method was used for survival analysis, and comparisons were performed using the log-rank test. Multivariable survival analyses were also performed to rule out dependent variables using Cox proportional hazards regression models. When the two-tailed *P* value was less than 0.05, the difference was considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics ver. 24 (IBM, Chicago IL, United States).

**RESULTS**

***Clinicopathological features***

We analysed a total of 77 patients with type 3 g-NETs (Table 1), aged between 28 and 79 years old, with a median age of 48 years. There were 34 male patients (44.2%) and 43 female patients (55.8%). The tumours were mainly located in the gastric fundus/body (64/77, 83.1%), and most of them were single lesions (64/77, 83.1%), with a median tumour size of 1.5 cm (0.8-3.5 cm). Of the 73 patients with a known endoscopic appearance, 45 of the tumours were polypoid lesions, accounting for 61.6%, 17 were ulcers (23.3%), and 11 were bulges (15.1%). Among the 34 tumours showing gastric wall invasion, most were localized in the mucosa (M) and submucosa (22/34, 64.7%), five (14.7%) had invaded the muscularis propria (MP), and seven (20.6%) had invaded beyond the MP. The median Ki67 index of 77 patients was 3% (1%-10%), and there were 37 patients with G1 NETs (48.1%), 31 with G2 NETs (40.3%), and 9 with G3 NETs (11.7%). In terms of staging, there were 30 (39%) stage I tumours, 12 (15.6%) stage II, 11 (14.3%) stage III, and 24 (31.2%) stage IV, respectively. In terms of metastatic status, 10 patients (13.0%) had lymph node metastases, and 24 (31.2%) had distant metastases.

***Treatment***

Among the 77 patients, 33 (42.9%) underwent endoscopic treatment, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), 17 (22.1%) underwent surgical treatment, 6 (7.8%) received somatostatin analogs, and 21 (27.3%) received chemotherapy-based comprehensive treatment (CBCT). Treatments for G1 NETs were mainly endoscopic treatment (29/37, 78.4%), while G2 and G3 NETs were treated by surgery (12/40, 30%) and CBCT (19/40, 47.5%). It is worth noting that among the 33 patients treated by endoscopic resection (consisting of patients with G1 [29/33, 87.9%] and G2 NETs [4/33 12.1%]), no tumour recurrence or tumour-related death was observed within a median follow-up period of 36 mo (30-57 mo). The tumour size of these patients did not exceed 2 cm (range: 0.2-1.8 cm), and the median Ki67 index was 1% (1%-10%). Among the 17 patients with available data on gastric wall invasion, the tumours were limited to the mucosa (7/17, 41.2%) and submucosa (10/17, 58.8%). The 33 patients with endoscopic treatment were all in the early stage of the disease (28 in stage I and 5 in stage II), and no lymph node metastasis or distant metastasis was observed (Table 2).

***Heterogeneity of type 3 g-NETs***

As shown in Table 1, type 3 g-NETs had significant heterogeneity. Patients with G1, G2, and G3 NETs had their own clinicopathological characteristics. They was a significant difference in terms of age, gender, tumour size, endoscopic appearance, depth of gastric wall invasion, lymph node metastasis, distant metastasis, and treatment. The median maximal tumour diameters of G2 and G3 NETs were 3 cm and 4 cm, respectively, which were significantly larger than that of G1 NETs (0.8 cm) (*P* < 0.001). In terms of endoscopic appearance, G2 and G3 NETs were mainly polypoid and ulcer-like lesions, while G1 NETs were mainly polypoid lesions (G2 *vs* G1 NETs, *P* = 0.001; G3 *vs* G1 NETs, *P* = 0.055). Compared with G1 NETs, G2 NETs had a higher proportion of invasion in the MP and beyond the MP (63.7% *vs* 15%, *P* = 0.014) and lymph node metastasis (22.6% *vs* 5.4%, *P* = 0.027). There were only two (5.4%) cases of G1 NETs with distant metastasis, while 15 (48.4%) and 7 (77.8%) cases of G2 and G3 NETs had distant metastasis (G2 *vs* G1 NETs, *P* < 0.001; G3 *vs* G1 NETs, *P* < 0.001). In terms of staging, the stage of G1 NETs patients was mostly early (stage I-II, 89.2%), while G2 and G3 NETs patients mostly had late stage (stage III-IV, 71% and 100%, respectively) (G2/G3 *vs* G1, *P* <0.001).

***Follow-up and analysis of prognostic factors***

With a median follow-up period of 35 mo (24-52 mo), the 3-year tumour-specific survival of patients with type 3 g-NETs was 75%. From the univariable analysis (Table 3), we can see that tumour size, endoscopic appearance, gastric wall invasion, grade, clinical stage, and treatment were significantly related to prognosis. Pathological grade [G3 *vs* G1, hazard ratio (95% confidence interval): 20.58 (1.942-218.11), *P* = 0.012] and distant metastasis [stage IV *vs* I-III, hazard ratio (95% confidence interval): 4.51 (1.10-18.41), *P* = 0.036] were independent risk factors affecting prognosis (Table 4). As shown in Figure 1A, there was a significant difference in the survival of patients with G1, G2, and G3 NETs (*P* < 0.001), with 3-year tumour-specific survival rates of 96%, 66%, and 17%, respectively. In addition, the median survival time of patients with G3 NETs was 27 mo, while that of patients with G1 and G2 NETs was not reached. As shown in Figure 1B, the prognosis of patients with distant metastasis was significantly better than that of patients without (*P* < 0.001). The median survival of patients with distant metastasis was 40 mo, while the median survival of patients without distant metastasis was not reached.

**DISCUSSION**

Type 3 g-NETs are a rare tumour with some clinicopathological characteristics and considered to be more aggressive[13-15]. With the increasing incidence of neuroendocrine neoplasms[1-3,16], it is gradually receiving attention from clinicians. The prognosis of type 3 g-NETs was worse with a 3-year survival rate of 75% in our study, while the survival rate of type 1 g-NETs was found to be almost 100%[17,18], followed by type 2 (60%-90%)[11].

There were several reasons for the malignant behavior and worse outcome of type 3 g-NETs. Unlike types 1 and 2 g-NETs, originating from enterochromaffin-like cells and stimulated by high serum gastrin with related background diseases, type 3 g-NETs were sporadic with no related diseases and normal gastrin levels. The origin of the cells in type 3 g-NETs are unclear yet, which may be derived from different neuroendocrine cells[9]. It may account for the poor prognosis of type 3 g-NETs. In addition, compared with types 1 and 2, type 3 g-NETs seemed to have a higher Ki67 index[19,20]. In our study, a higher Ki67 index was negatively correlated with the prognosis of type 3 g-NETs. Different molecular mechanisms have been described between well-differentiated NET and poorly differentiated NEC[21]. Patients with type 1 g-NETs have been found to have an association with mutations in *ATP4A* and *PTH1R*[22-24], while type 2 g-NETs has been associated with mutations in the *MEN-1* gene[25]. However, there are fewer studies related to type 3 g-NETs. Some small sample studies have found that *p53* gene expression exists in type 3 g-NETs and has a negative correlation with prognosis[26,27]. *p53* was also shown to be one of the commonly mutated genes in gastric NEC[28,29], illustrating that type 3 g-NETs share some similarities to g-NEC, explaining the poor prognosis of type 3 g-NETs. However, more research is required to support the above as the molecular mechanism of type 3 g-NETs.

Well-differentiated g-NETs are heterogeneous, but the heterogeneity of type 3 g-NETs has not been well described. And we did find well-differentiated G3 NETs and confirmed its unique feature among type 3 g-NETs. In our study, G1, G2, and G3 NETs had their own clinical pathological characteristics (Table 1), illuminating their heterogeneity based on the 2019 WHO pathological classification. Additionally, G1 NETs were common (37/77, 48.1%), not rare as previously reported[9]. Furthermore, G1 NETs showed a low metastasis rate [4 patients (10.8%) with lymph node metastases and 2 (5.4%) with distant metastases] and good prognosis (3-year tumour-specific survival rate: 96%). However, G2 and G3 NETs had higher lymph node metastasis rates and distant metastasis rates, and their prognoses were worse. Also, multivariable analysis also confirmed that G3 was an independent risk factor affecting prognosis. Well-differentiated G3 NETs were reported in gastroenteropancreatic NENs in several studies[30-32] and had their own morphological characteristics and pathways differing from NECs[21,30]. It seems wise to add G3 to well-differentiated NETs in the WHO 2019 neuroendocrine tumour grading system. This indicates that G3 NETs has more aggressive biological behavior than G1 and G2 NETs and pathological grade has an effective prognostic role on outcome for NETs. Surprisingly, as early as 2013, Chinese pathologists also proposed a similar classification[33].

Indeed, type 3 g-NETs showed more malignant biological behavior with a metastasis rate of 44.2%, which was similar to that reported in the literature[19,20], including 10 patients with regional lymph node metastasis (13.0%) and 24 with distant metastasis (31.2%). The 3-year tumour-specific survival with lymph node metastasis and distant metastasis was 70% and 35%, respectively, which was significantly associated with prognosis (*P* < 0.001). Additionally, distant metastasis was an independent risk factor affecting prognosis. Studies related to prognosis for type 3 g-NETs were scare, but several studies of gastroenteropancreatic NETs[34-36] had shown that distant metastasis was significantly associated with prognosis.

Treatment strategies for type 3 NETs are varied for heterogeneity[11,15] and the grade and stage need to be considered to make an optimal treatment for type 3 NETs. In our study, advanced G3 NET patients (6/7) received CBCT, while G1 and G2 NETs patients with early-stage disease underwent endoscopic treatment. Thirty-three patients treated endoscopically had no tumour recurrence or tumour-related death during a median follow-up period of 36 mo (Table 2). A South Korean study of 50 cases of endoscopic treatment of type 3 g-NETs found no evidence of tumour recurrence in the pathological complete resection group or incomplete resection group during a median follow-up period of 43.73 mo[37]. Another study involving 22 patients in South Korea reported that only one case of lymph node metastasis was found within a median follow-up period of 59 mo after endoscopic treatment[38]. Also, a retrospective multicentre study from Japan reported that of 48 patients treated by endoscopic resection alone, only one developed recurrence with a median follow-up period of 32 mo[39]. These studies suggested that endoscopic treatment was safe and effective for tumours smaller than 2 cm, 1.5 cm, and 1cm, respectively, confined to the mucosa and submucosa in type 3 gastric NETs. This may give us a clinical hint: For G1 and G2 NETs patients with a tumour size < 2 cm, confined to the mucosa and submucosa, endoscopic resection (EMR and ESD) should be considered.

This study also has several limitations. The patients in this study came from four NET centres, and the pathological diagnoses were made by different pathologists. Furthermore, the pathological grading system was updated in 2019. To solve this problem, all pathological diagnoses were reviewed by the same NET pathologist with more than 30 years of experience. Also, a few specimens obtained from endoscopic/EUS biopsy may be too small or deformed, which had an effect on assessment of Ki67 index and number of mitoses. In addition, missing data from some of the patients may have introduced some information bias, and suitable analyses were used to avoid it.

**CONCLUSION**

Type 3 g-NETs have a relatively malignant biological behavior with a poor prognosis and strong heterogeneity. G1, G2, and G3 NETs have their own clinicopathological characteristics and distinctive prognoses. The 2019 WHO pathological grade and distant metastasis are independent risk factors affecting prognosis. In addition, the 2019 WHO pathological classification is useful for assessing the biological behavior and prognosis of type 3 g-NETs. Treatment is related to the grade and stage of the tumours. Endoscopic treatment is safe and effective for G1 NETs patients with type 3 g-NETs having tumours smaller than 2 cm and limited to the mucosa and submucosa.

**ARTICLE HIGHLIGHTS**

***Research background***

Given the rarity, type 3 gastric neuroendocrine tumours (g-NETs) have not been well described.

***Research motivation***

The pathological classification of gastroenteropancreatic neuroendocrine neoplasms was updated in 2019. Well-differentiated NET G3 was added, but its role has not been yet illustrated in type 3 g-NETs.

***Research objectives***

We dedicated to illustrate clinicopathological features and outcome of type 3 g-NETs. Also, we aimed to assess the role of the updated WHO pathological classification in type 3 g-NETs.

***Research methods***

Data of patients with type 3 g-NETs from four NET centres in China were collected and analysed retrospectively

***Research results***

Seventy-seven patients with type 3 g-NETs were enrolled. Of these, there were 37 G1 tumours (48.1%), 31 G2 (40.3%), and 9 G3 (11.7%). Compared with G1 NETs, G2 NETs had a higher lymph node metastasis rate, and G3 NETs had a higher distant metastasis rate. In terms of treatment, 33 patients (29 G1 and 4 G2 ) with stage I/II disease underwent endoscopic treatment, and no one had tumour recurrence or tumour-related death with a median follow-up period of 36 mo. Additionally, grade and distant metastasis were independent risk factors for prognosis in multivariable analysis.

***Research conclusions***

Type 3 g-NETs is heterogeneous with unique clinicopathological features and the 2019 WHO pathological classification is effective to predict their biological behaviors and prognosis. Besides, endoscopic resection is safe and effective for G1 NETs with tumours under 2 cm and confined to the mucosa or submucosa.

***Research perspectives***

Having a better understanding of the clinicopathological characteristics and outcome of type 3 g-NETs based on the 2019 WHO pathological classification, clinicians could offer an optimal treatment for patients. Grade and stage are related to outcome and should be considered before treatment. In addition, endoscopic treatment is effective and should be considered for small, low grade, superficial tumours.

**ACKNOWLEDGEMENTS**

We are grateful to the data collectors at each NET centre.

**REFERENCES**

1 **Scherübl H**, Cadiot G, Jensen RT, Rösch T, Stölzel U, Klöppel G. Neuroendocrine tumors of the stomach (gastric carcinoids) are on the rise: small tumors, small problems? *Endoscopy* 2010; **42**: 664-671 [PMID: 20669078 DOI: 10.1055/s-0030-1255564]

2 **Ellis L**, Shale MJ, Coleman MP. Carcinoid tumors of the gastrointestinal tract: trends in incidence in England since 1971. *Am J Gastroenterol* 2010; **105**: 2563-2569 [PMID: 20823835 DOI: 10.1038/ajg.2010.341]

3 **Dasari A**, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao JC. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol* 2017; **3**: 1335-1342 [PMID: 28448665 DOI: 10.1001/jamaoncol.2017.0589]

4 **Gastrointestinal Pathology Study Group of Korean Society of Pathologists**, Cho MY, Kim JM, Sohn JH, Kim MJ, Kim KM, Kim WH, Kim H, Kook MC, Park DY, Lee JH, Chang H, Jung ES, Kim HK, Jin SY, Choi JH, Gu MJ, Kim S, Kang MS, Cho CH, Park MI, Kang YK, Kim YW, Yoon SO, Bae HI, Joo M, Moon WS, Kang DY, Chang SJ. Current Trends of the Incidence and Pathological Diagnosis of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs) in Korea 2000-2009: Multicenter Study. *Cancer Res Treat* 2012; **44**: 157-165 [PMID: 23091441 DOI: 10.4143/crt.2012.44.3.157]

5 **Niederle MB**, Hackl M, Kaserer K, Niederle B. Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters. *Endocr Relat Cancer* 2010; **17**: 909-918 [PMID: 20702725 DOI: 10.1677/ERC-10-0152]

6 **O'Connor JM**, Marmissolle F, Bestani C, Pesce V, Belli S, Dominichini E, Mendez G, Price P, Giacomi N, Pairola A, Loria FS, Huertas E, Martin C, Patane K, Poleri C, Rosenberg M, Cabanne A, Kujaruk M, Caino A, Zamora V, Mariani J, Dioca M, Parma P, Podesta G, Andriani O, Gondolesi G, Roca E. Observational study of patients with gastroenteropancreatic and bronchial neuroendocrine tumors in Argentina: Results from the large database of a multidisciplinary group clinical multicenter study. *Mol Clin Oncol* 2014; **2**: 673-684 [PMID: 25054030 DOI: 10.3892/mco.2014.332]

7 **Rindi G**, Luinetti O, Cornaggia M, Capella C, Solcia E. Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. *Gastroenterology* 1993; **104**: 994-1006 [PMID: 7681798 DOI: 10.1016/0016-5085(93)90266-f]

8 **Ruszniewski P**, Delle Fave G, Cadiot G, Komminoth P, Chung D, Kos-Kudla B, Kianmanesh R, Hochhauser D, Arnold R, Ahlman H, Pauwels S, Kwekkeboom DJ, Rindi G; Frascati Consensus Conference; European neuroendocrine Tumor Society. Well-differentiated gastric tumors/carcinomas. *Neuroendocrinology* 2006; **84**: 158-164 [PMID: 17312375 DOI: 10.1159/000098007]

9 **Nagtegaal ID**, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, Washington KM, Carneiro F, Cree IA; WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2020; **76**: 182-188 [PMID: 31433515 DOI: 10.1111/his.13975]

10 **Basuroy R**, Srirajaskanthan R, Prachalias A, Quaglia A, Ramage JK. Review article: the investigation and management of gastric neuroendocrine tumours. *Aliment Pharmacol Ther* 2014; **39**: 1071-1084 [PMID: 24628514 DOI: 10.1111/apt.12698]

11 **Delle Fave G**, O'Toole D, Sundin A, Taal B, Ferolla P, Ramage JK, Ferone D, Ito T, Weber W, Zheng-Pei Z, De Herder WW, Pascher A, Ruszniewski P; Vienna Consensus Conference participants. ENETS Consensus Guidelines Update for Gastroduodenal Neuroendocrine Neoplasms. *Neuroendocrinology* 2016; **103**: 119-124 [PMID: 26784901 DOI: 10.1159/000443168]

12 **Doescher J,** Veit JA, Hoffmann TK. The 8th edition of the AJCC Cancer Staging Manual. *HNO* 2017; **65:** 956-961 [DOI: 10.1007/s00106-017-0391-3]

13 **Rindi G**, Bordi C, Rappel S, La Rosa S, Stolte M, Solcia E. Gastric carcinoids and neuroendocrine carcinomas: pathogenesis, pathology, and behavior. *World J Surg* 1996; **20**: 168-172 [PMID: 8661813 DOI: 10.1007/s002689900026]

14 **Rindi G**, Azzoni C, La Rosa S, Klersy C, Paolotti D, Rappel S, Stolte M, Capella C, Bordi C, Solcia E. ECL cell tumor and poorly differentiated endocrine carcinoma of the stomach: prognostic evaluation by pathological analysis. *Gastroenterology* 1999; **116**: 532-542 [PMID: 10029611 DOI: 10.1016/s0016-5085(99)70174-5]

15 **Pfister D,** Ang K, Brizel D. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. 2019. Available from: <http://ci.nii.ac.jp/naid/10030762657>

16 **Cao LL**, Lu J, Lin JX, Zheng CH, Li P, Xie JW, Wang JB, Chen QY, Lin M, Tu RH, Huang CM. Incidence and survival trends for gastric neuroendocrine neoplasms: An analysis of 3523 patients in the SEER database. *Eur J Surg Oncol* 2018; **44**: 1628-1633 [PMID: 29983275 DOI: 10.1016/j.ejso.2018.01.082]

17 **Chen WC**, Warner RR, Ward SC, Harpaz N, Divino CM, Itzkowitz SH, Kim MK. Management and disease outcome of type I gastric neuroendocrine tumors: the Mount Sinai experience. *Dig Dis Sci* 2015; **60**: 996-1003 [PMID: 25399327 DOI: 10.1007/s10620-014-3410-1]

18 **Sato Y**, Imamura H, Kaizaki Y, Koizumi W, Ishido K, Kurahara K, Suzuki H, Fujisaki J, Hirakawa K, Hosokawa O, Ito M, Kaminishi M, Furuta T, Chiba T, Haruma K. Management and clinical outcomes of type I gastric carcinoid patients: retrospective, multicenter study in Japan. *Dig Endosc* 2014; **26**: 377-384 [PMID: 24188531 DOI: 10.1111/den.12197]

19 **Lee HE**, Mounajjed T, Erickson LA, Wu TT. Sporadic Gastric Well-Differentiated Neuroendocrine Tumors Have a Higher Ki-67 Proliferative Index. *Endocr Pathol* 2016; **27**: 259-267 [PMID: 27306997 DOI: 10.1007/s12022-016-9443-6]

20 **Vanoli A**, La Rosa S, Miceli E, Klersy C, Maragliano R, Capuano F, Persichella A, Martino M, Inzani F, Luinetti O, Di Sabatino A, Sessa F, Paulli M, Corazza GR, Rindi G, Bordi C, Capella C, Solcia E. Prognostic Evaluations Tailored to Specific Gastric Neuroendocrine Neoplasms: Analysis Of 200 Cases with Extended Follow-Up. *Neuroendocrinology* 2018; **107**: 114-126 [PMID: 29895024 DOI: 10.1159/000489902]

21 **Tang LH**, Untch BR, Reidy DL, O'Reilly E, Dhall D, Jih L, Basturk O, Allen PJ, Klimstra DS. Well-Differentiated Neuroendocrine Tumors with a Morphologically Apparent High-Grade Component: A Pathway Distinct from Poorly Differentiated Neuroendocrine Carcinomas. *Clin Cancer Res* 2016; **22**: 1011-1017 [PMID: 26482044 DOI: 10.1158/1078-0432.CCR-15-0548]

22 **Calvete O**, Reyes J, Zuñiga S, Paumard-Hernández B, Fernández V, Bujanda L, Rodriguez-Pinilla MS, Palacios J, Heine-Suñer D, Banka S, Newman WG, Cañamero M, Pritchard DM, Benítez J. Exome sequencing identifies ATP4A gene as responsible of an atypical familial type I gastric neuroendocrine tumour. *Hum Mol Genet* 2015; **24**: 2914-2922 [PMID: 25678551 DOI: 10.1093/hmg/ddv054]

23 **Calvete O**, Herraiz M, Reyes J, Patiño A, Benitez J. A cumulative effect involving malfunction of the PTH1R and ATP4A genes explains a familial gastric neuroendocrine tumor with hypothyroidism and arthritis. *Gastric Cancer* 2017; **20**: 998-1003 [PMID: 28474257 DOI: 10.1007/s10120-017-0723-8]

24 **Benítez J**, Marra R, Reyes J, Calvete O. A genetic origin for acid-base imbalance triggers the mitochondrial damage that explains the autoimmune response and drives to gastric neuroendocrine tumours. *Gastric Cancer* 2020; **23**: 52-63 [PMID: 31250150 DOI: 10.1007/s10120-019-00982-4]

25 **Debelenko LV**, Emmert-Buck MR, Zhuang Z, Epshteyn E, Moskaluk CA, Jensen RT, Liotta LA, Lubensky IA. The multiple endocrine neoplasia type I gene locus is involved in the pathogenesis of type II gastric carcinoids. *Gastroenterology* 1997; **113**: 773-781 [PMID: 9287968 DOI: 10.1016/s0016-5085(97)70171-9]

26 **Peny MO**, Donckier V, Gelin M, Haot J, Noel JC. Sporadic carcinoid of the stomach: a highly proliferative disease with a probable role for p53 protein dysregulation. *Eur J Gastroenterol Hepatol* 1999; **11**: 677-679 [PMID: 10418942 DOI: 10.1097/00042737-199906000-00016]

27 **Safatle-Ribeiro AV**, Ribeiro U Jr, Corbett CE, Iriya K, Kobata CH, Sakai P, Yagi OK, Pinto PE Jr, Zilberstein B, Gama-Rodrigues J. Prognostic value of immunohistochemistry in gastric neuroendocrine (carcinoid) tumors. *Eur J Gastroenterol Hepatol* 2007; **19**: 21-28 [PMID: 17206073 DOI: 10.1097/01.meg.0000250582.30737.bd]

28 **Makuuchi R**, Terashima M, Kusuhara M, Nakajima T, Serizawa M, Hatakeyama K, Ohshima K, Urakami K, Yamaguchi K. Comprehensive analysis of gene mutation and expression profiles in neuroendocrine carcinomas of the stomach. *Biomed Res* 2017; **38**: 19-27 [PMID: 28239029 DOI: 10.2220/biomedres.38.19]

29 **von Arx C**, Capozzi M, López-Jiménez E, Ottaiano A, Tatangelo F, Di Mauro A, Nasti G, Tornesello ML, Tafuto S. Updates on the Role of Molecular Alterations and NOTCH Signalling in the Development of Neuroendocrine Neoplasms. *J Clin Med* 2019; **8**: [PMID: 31443481 DOI: 10.3390/jcm8091277]

30 **Milione M**, Maisonneuve P, Spada F, Pellegrinelli A, Spaggiari P, Albarello L, Pisa E, Barberis M, Vanoli A, Buzzoni R, Pusceddu S, Concas L, Sessa F, Solcia E, Capella C, Fazio N, La Rosa S. The Clinicopathologic Heterogeneity of Grade 3 Gastroenteropancreatic Neuroendocrine Neoplasms: Morphological Differentiation and Proliferation Identify Different Prognostic Categories. *Neuroendocrinology* 2017; **104**: 85-93 [PMID: 26943788 DOI: 10.1159/000445165]

31 **Heetfeld M**, Chougnet CN, Olsen IH, Rinke A, Borbath I, Crespo G, Barriuso J, Pavel M, O'Toole D, Walter T; other Knowledge Network members. Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer* 2015; **22**: 657-664 [PMID: 26113608 DOI: 10.1530/ERC-15-0119]

32 **Pellat A**, Coriat R. Well Differentiated Grade 3 Neuroendocrine Tumors of the Digestive Tract: A Narrative Review. *J Clin Med* 2020; **9**: [PMID: 32492939 DOI: 10.3390/jcm9061677]

33 **Neuroendocrine Neoplasms Editorial Board**. Neuroendocrine neoplasms 2013 Standardization in diagnosis of gastrointestinal and pancreatic neuroendocrine neoplasms: the Chinese consensus. *Chin J Pathol* 2013; **42:** 691-694 [DOI: 10.3760/cma.j.issn.0529-5807.2013.10.011]

34 **Zheng Z**, Chen C, Jiang L, Zhou X, Dai X, Song Y, Li Y. Incidence and risk factors of gastrointestinal neuroendocrine neoplasm metastasis in liver, lung, bone, and brain: A population-based study. *Cancer Med* 2019; **8**: 7288-7298 [PMID: 31609098 DOI: 10.1002/cam4.2567]

35 **Panzuto F**, Pusceddu S, Faggiano A, Rinzivillo M, Brighi N, Prinzi N, Riccardi F, Iannicelli E, Maggio I, Femia D, Tafuto S, Manuzzi L, Di Sarno A, Annibale B, de Braud F, Campana D; Itanet (Italian Association for Neuroendocrine Tumours). Prognostic impact of tumour burden in stage IV neuroendocrine neoplasia: A comparison between pancreatic and gastrointestinal localizations. *Pancreatology* 2019; **19**: 1067-1073 [PMID: 31587962 DOI: 10.1016/j.pan.2019.09.015]

36 **Wang Z**, Li W, Chen T, Yang J, Luo L, Zhang L, Sun B, Liang R. Retrospective analysis of the clinicopathological characteristics of gastrointestinal neuroendocrine neoplasms. *Exp Ther Med* 2015; **10**: 1084-1088 [PMID: 26622444 DOI: 10.3892/etm.2015.2634]

37 **Kwon YH**, Jeon SW, Kim GH, Kim JI, Chung IK, Jee SR, Kim HU, Seo GS, Baik GH, Choi KD, Moon JS. Long-term follow up of endoscopic resection for type 3 gastric NET. *World J Gastroenterol* 2013; **19**: 8703-8708 [PMID: 24379589 DOI: 10.3748/wjg.v19.i46.8703]

38 **Min BH**, Hong M, Lee JH, Rhee PL, Sohn TS, Kim S, Kim KM, Kim JJ. Clinicopathological features and outcome of type 3 gastric neuroendocrine tumours. *Br J Surg* 2018; **105**: 1480-1486 [PMID: 29893418 DOI: 10.1002/bjs.10901]

39 **Hirasawa T**, Yamamoto N, Sano T. Is endoscopic resection appropriate for type 3 gastric neuroendocrine tumors? Retrospective multicenter study. *Dig Endosc* 2020 [PMID: 32578248 DOI: 10.1111/den.13778]

**Footnotes**

**Institutional review board statement:** The study was reviewed and approved by the clinical research ethics committee of the China-Japan Friendship Hospital (No. 2019-24-K18-1).

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** The authors declare that no competing interests exist.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Noncommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** July 11, 2020

**First decision:** September 17, 2020

**Article in press:**

**Specialty type:** Oncology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): B, B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): E

**P-Reviewer:** Balaban DV, Cunningham M, Kim DK, Nagai S, Skok P **S-Editor:** Fan JR **L-Editor:** Wang TQ **P-Editor:**

**Figure Legends**



**Figure 1 Kaplan-meier curves of patients with type 3 gastric neuroendocrine tumours.** A: Grade; B: Stage.

**Table 1 Clinicopathological features of type 3 gastric neuroendocrine tumours**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Total, *n* (%)** | **G1 NETs, *n* (%)** | **G2 NETs, *n* (%)** | **G3 NETs, *n* (%)** | ***P* value** | **G2 *vs* G1** | **G3 *vs* G1** | **G3 *vs* G2** |
| Number | 77 (100) | 37 (48.1) | 31 (40.3) | 9 (11.7) |  |  |  |  |
| Age (range) | 48 (28-79) | 47 (29-79) | 47.5 (28-78) | 62 (33-68) | 0.048 | 1 | 0.077 | 0.049 |
| Gender |  |  |  |  | 0.016 | 1.000 | 0.011 | 0.039 |
| male | 34 (44.2) | 13 (35.1) | 13 (41.9) | 8 (88.9) |  |  |  |  |
| female | 43 (55.8) | 24 (64.9) | 18 (58.1) | 1 (11.1) |  |  |  |  |
| Size (cm) | 1.5 (0.8-3.5) | 0.8 (0.5-1.2) | 3 (1.5-5) | 4 (2.5-5.25) | < 0.001 | < 0.001 | < 0.001 | 1.000 |
| Site |  |  |  |  | 0.122 |  |  |  |
| cardia | 10 (13) | 2 (5.4) | 6 (19.4) | 2 (22.2) |  |  |  |  |
| fundus/body | 64 (83.1) | 34 (91.9) | 24 (77.4) | 6 (66.7) |  |  |  |  |
| antrum | 3 (3.9) | 1 (2.7) | 1 (3.2) | 1 (11.1) |  |  |  |  |
| Number |  |  |  |  | 0.087 |  |  |  |
| 1 | 64 (83.1) | 27 (73) | 28 (90.3) | 9 (100) |  |  |  |  |
| ≥ 2 | 13 (16.9) | 10 (27) | 3 (9.7) | 0 |  |  |  |  |
| EA |  |  |  |  | 0.002 | 0.001 | 0.055 | 1.000 |
| polyp | 45 (61.6) | 29 (82.9) | 12 (41.4) | 4 (44.4) |  |  |  |  |
| bulge | 11 (15.1) | 4 (11.4) | 6 (20.7) | 1 (11.1) |  |  |  |  |
| ulcer | 17 (23.3) | 2 (5.7) | 11 (37.9) | 4 (44.4) |  |  |  |  |
| unknown | 4 | 2 | 2 | 0 |  |  |  |  |
| Infiltration |  |  |  |  | 0.014 | 0.014 | 0.290 | 1.000 |
| M/SM | 22 (64.7) | 17 (85.0) | 4 (36.4) | 1 (33.3) |  |  |  |  |
| MP | 5 (14.7) | 2 (10) | 2 (18.2) | 1 (33.3) |  |  |  |  |
| beyond MP | 7 (20.6) | 1 (5.0) | 5 (45.5) | 1 (33.3) |  |  |  |  |
| unknown | 43 | 17 | 20 | 6 |  |  |  |  |
| Ki67 (%)  | 3 (1-10) | 1 (1-1) | 8 (4-10) | 30 (25-37.5) | < 0.001 | < 0.001 | < 0.001 | 0.047 |
| LNM only | 10 (13.0) | 2 (5.4) | 7 (22.6) | 1 (11.1) | < 0.001 | 0.027 | 0.439 | 1.000 |
| DM | 24 (31.2) | 2 (5.4) | 15 (48.4) | 7 (77.7) | < 0.001 | < 0.001 | < 0.001 | 0.288 |
| Stage |  |  |  |  | < 0.001 | < 0.001 | < 0.001 | 0.494 |
| I | 30 (39.0) | 26 (70.3) | 4 (12.9) | 0 |  |  |  |  |
| II | 12 (15.6) | 7 (18.9) | 5 (16.1) | 0 |  |  |  |  |
| III | 11 (14.3) | 2 (5.4) | 7 (22.6) | 2 (22.2) |  |  |  |  |
| IV | 24 (31.2) | 2 (5.4) | 15 (48.4) | 7 (77.8) |  |  |  |  |
| Treatment |  |  |  |  | < 0.001 | < 0.001 | < 0.001 | 0.510 |
| ER | 33 (42.9) | 29 (78.4) | 4 (12.9) | 0 |  |  |  |  |
| surgery | 17 (22.1) | 5 (13.5) | 10 (32.3) | 2 (22.2) |  |  |  |  |
| SSA | 6 (7.8) | 1 (2.7) | 4 (12.9) | 1 (11.1) |  |  |  |  |
| CBCT | 21 (27.3) | 2 (5.4) | 13 (41.9) | 6 (66.7) |  |  |  |  |

NET: Neuroendocrine tumour; SD: Standard deviation; EA: Endoscopic appearance; M: Mucosa; SM: Submucosa; MP: Muscularis propria; ER: Endoscopic resection; LNM: Lymph node metastasis; DM: Distant metastasis; SSA: Somatostatin analogs; CBCT: Chemotherapy-based comprehensive treatment.

**Table 2 Characteristics of patients with endoscopic resection**

|  |  |
| --- | --- |
|  | **Endoscopic resection (*n* = 33), *n* (%)** |
| Size, median (25th–75th percentile), cm (range) | 0.7 (0.5-1.1); (0.2-1.8) |
| Infiltration |  |
| M/SM | 17 (100%) |
| MP/beyond MP | 0 |
| Unknown | 16 |
| Ki67, median (25th–75th percentile), % | 1 (1-10) |
| Grade |  |
| G1 | 29 (87.9) |
| G2 | 4 (12.1) |
| G3 | 0 |
| Stage |  |
| I | 28 (84.8) |
| II | 5 (15.2) |
| III-IV | 0 |
| Recurrence or cancer-specific death | 0 |

M: Mucosa; SM: Submucosa; MP: Muscularis propria.

**Table 3 Univariate analysis for prognosis**

|  |  |  |
| --- | --- | --- |
|  | **HR (95%CI)** | ***P* value** |
| Age  |  |  |
| ≤ 45 years old | 1 |  |
| > 45 years old | 1.92 (0.61-6.06) | 0.264 |
| Gender |  |  |
| male | 1 |  |
| female  | 0.87 (0.32-2.41) | 0.794 |
| Size |  |  |
| < 2 cm | 1 |  |
| ≥ 2 cm | 10.07 (2.27-44.67) | 0.002 |
| Site |  |  |
| cardia | 1 |  |
| fundus/body | 0.88 (0.20-3.98) | 0.871 |
| antrum | 5.817 (0.81-42.01) | 0.081 |
| Number |  |  |
| 1 | 1 |  |
| ≥2 | 0.33 (0.04-2.48) | 0.279 |
| EA |  |  |
| polyp | 1 |  |
| bulge | 2.37 (0.45-12.54) | 0.312 |
| ulcer | 4.20 (1.33-13.23) | 0.014 |
| Infiltration |  |  |
| M/SM | 1 |  |
| MP | 8.57 (0.77-95.33) | 0.081 |
| beyond MP | 3.02 (0.19-48.42) | 0.436 |
| Grade |  |  |
| G1 | 1 |  |
| G2 | 9.77 (1.22-78.10) | 0.032 |
| G3 | 61.68 (7.01-542.62) | < 0.001 |
| Stage |  |  |
| I-III | 1 |  |
| IV | 11.15 (3.13-39.66) | < 0.001 |
| Treatment |  |  |
| ER or surgery | 1 |  |
| SSA | 4.65 (0.47-45.57) | 0.187 |
| CBCT | 11.38 (3.16-40.93) | < 0.001 |

EA: Endoscopic appearance; M: Mucosa; SM: Submucosa; MP: Muscularis propria; ER: Endoscopic resection; SSA: Somatostatin analogs; CBCT: Chemotherapy-based comprehensive treatment.

**Table 4 Multivariate analysis for prognosis**

|  |  |  |
| --- | --- | --- |
|  | **HR (95%CI)** | ***P* value** |
| Grade |  |  |
| G1 | 1 |  |
| G2 | 4.923 (0.55-43.76) | 0.153 |
| G3 | 20.58 (1.942-218.11) | 0.012 |
| Stage |  |  |
| I-III | 1 |  |
| IV | 4.51 (1.10-18.41) | 0.036 |