

# World Journal of *Gastrointestinal Oncology*

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Retrospective Study

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

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### 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

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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

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**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.

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## 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<sup>[1,2]</sup>. 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<sup>[3]</sup>. In South Korea, Austria, and Argentina, g-NENs accounted for 14.6%, 23%, and 6.9% of gastrointestinal and pancreatic neuroendocrine tumours, respectively<sup>[4-6]</sup>.

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<sup>[7-9]</sup>. 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<sup>[10,11]</sup>. 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 lesions 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  $^{68}\text{Ga}$  DOTATATE positron emission tomography/computed tomography to assess the status of lymph node and distant metastases.

### Pathological classification and tumor node metastasis staging

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

### 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

Table 1 Clinicopathological features of type 3 gastric neuroendocrine tumours

	Total, <i>n</i> (%)	G1 NETs, <i>n</i> (%)	G2 NETs, <i>n</i> (%)	G3 NETs, <i>n</i> (%)	<i>P</i> 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.

(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. There 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 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<sup>[13-15]</sup>. With the increasing incidence of neuroendocrine



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

	Endoscopic resection (n = 33), n (%)
Size, median (25 <sup>th</sup> -75 <sup>th</sup> 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 (25 <sup>th</sup> -75 <sup>th</sup> 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.

neoplasms<sup>[1-3,16]</sup>, 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%<sup>[17,18]</sup>, followed by type 2 (60%-90%)<sup>[11]</sup>.

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<sup>[9]</sup>. 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<sup>[19,20]</sup>. 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<sup>[21]</sup>. Patients with type 1 g-NETs have been found to have an association with mutations in *ATP4A* and *PTH1R*<sup>[22-24]</sup>, while type 2 g-NETs has been associated with mutations in the *MEN-1* gene<sup>[25]</sup>. 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<sup>[26,27]</sup>. *p53* was also shown to be one of the commonly mutated genes in gastric NEC<sup>[28,29]</sup>, illustrating that type 3 g-NETs share some similarities to g-NEC, explaining the poor prognosis of type 3 g-NETs. However, more researches are 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<sup>[9]</sup>. 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<sup>[30-32]</sup> and had their own morphological characteristics and pathways differing

**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.

from NECs<sup>[21,30]</sup>. 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<sup>[33]</sup>.

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

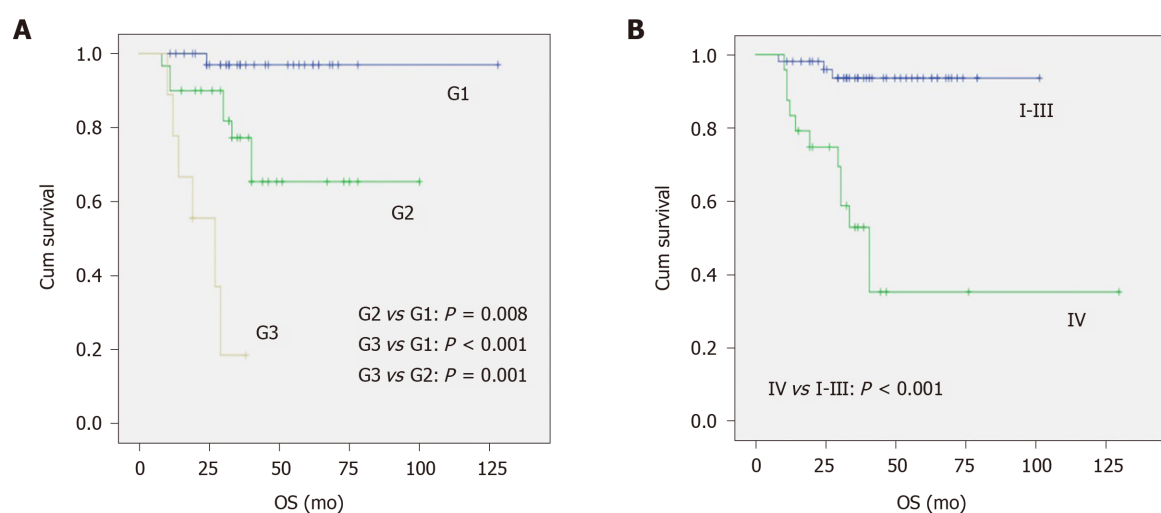


Figure 1 Kaplan-meier curves of patients with type 3 gastric neuroendocrine tumours. A: Grade; B: Stage. OS: Overall survival.

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<sup>[19,20]</sup>, 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 scarce, but several studies of gastroenteropancreatic NETs<sup>[34-36]</sup> had shown that distant metastasis was significantly associated with prognosis.

Treatment strategies for type 3 NETs are varied for heterogeneity<sup>[11,15]</sup> 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<sup>[37]</sup>. 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<sup>[38]</sup>. 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<sup>[39]</sup>. These studies suggested that endoscopic treatment was safe and effective for tumours smaller than 2 cm, 1.5 cm, and 1 cm, 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.



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