Personalized treatment of well-differentiated gastric neuroendocrine tumors based on clinicopathological classification and grading: A multicenter retrospective study

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Abstract

Background: The incidence of well-differentiated gastric neuroendocrine tumors (G-NET) is increasing annually, and while they have a good prognosis and low mortality rate, their high recurrence rate makes treatment options controversial. This study aims to determine the relationship between individualized treatment plans and the recurrence of G-NET.

Methods: We performed a multicenter, retrospective study of 94 patients with highly differentiated G-NET and treated at Peking Union Medical College Hospital, Yantai Yuhuangding Hospital, and Beijing Zhong-Neng-Jian Hospital from November 2015 to September 2023. Risk factors for recurrence of G-NETs were investigated using chi-squared test and multifactorial logistic regression analysis.

Results: After a median follow-up of 49 months, the overall recurrence rate among the 94 G-NET patients was 14% (13/94). The recurrence rates of endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), somatostatin analog (SSA) therapy, and surgery were 43% (6/14), 10% (5/49), 5% (1/22), and 11% (1/9), respectively. Post-treatment recurrence rates were significantly different ($P = 0.014$) among four treatments (EMR, ESD, SSA, and surgery), and further subgroup comparisons revealed lower recurrence rates in the ESD and SSA groups than in the EMR group. From the second month onward, SSA therapy considerably reduced the gastrin levels from 1081.0 (571.5, 2472.8) pg/mL to 461.5 (255.3, 795.0) pg/mL ($Z = –3.521$, $P < 0.001$). Both chi-squared test and multifactorial logistic regression analysis suggested that among the clinicopathological parameters studied, only the pre-treatment gastrin level ($P = 0.018$ and 0.005) and the type of treatment ($P = 0.014$ and 0.017) were significantly associated with G-NET recurrence.

Conclusions: Individualized treatment strategies may reduce the risk of relapse after G-NET treatment. Long-term SSA therapy may be a secure and efficacious treatment option for type 1 G-NET with more than six lesions, and it substantially decreases the incidence of post-treatment recurrence.

Keywords: Well-differentiated G-NET; Serum gastrin; Personalized treatment; Endoscopic submucosal dissection; Endoscopic mucosal resection; Somatostatin analog therapy; Surgical resection; Recurrence

Introduction

Neuroendocrine neoplasms (NENs) are a diverse category of neoplasms that develop from stem cells. They are characterized by neuroendocrine markers as well as the ability to release polypeptide hormones and/or bioactive amines.[1] During the past few decades, the global incidence of NENs has considerably increased. According to an update of the Surveillance, Epidemiology, and End Results (SEER) database, the incidence of NENs increased by more than six times from 1997 to 2012.[2]

In a recent study, the incidence and survival rates of NENs were compared between China and the United States. Although the incidence of NENs in China was lower (1.14 per 100,000 population) than that in the United States (6.26 per 100,000 population), the incidence in China increased more dramatically (9.8% *vs.* 3.6% per year, respectively).[3] The stomach is the third most common primary tumor site of NENs in China, and gastric NENs (G-NEN) displayed a similar upward trend in incidence. According to recent epidemiological data, G-NEN comprise 19.7% of all NENs in China,

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with a prevalence of around 0.23 per 100,000 population.[4]

The classification of G-NEN was changed in the most recent World Health Organization (WHO) Digestive Tumors Classification. Based on their tumor morphology, G-NEN are classified into well-differentiated neuroendocrine tumor (NET) (any grade), poorly differentiated neuroendocrine carcinoma, and mixed neuroendocrine–non-NEN.[5,6] In accordance with their etiology and histopathologic characteristics, gastric NETs (G-NET) are further divided into three basic categories, each of which has a unique biological behavior and prognosis.[7,8]

Although highly differentiated G-NET are typically low in malignancy and grow slowly, several studies have shown a high risk of tumor recurrence.[9,10] Even with successful treatment, the post-treatment recurrence rate within the first year can be as high as 5%–67%, with a median recurrence time of 8–35 months.[9] Various studies have suggested that the recurrence of G-NET may be related to factors such as tumor size, pathologic grade, and treatment modality, but conclusions vary widely.[9,10] The highly heterogeneous nature of G-NET and their high rate of recurrence after treatment make current treatment options a matter of controversy. Although many guidelines recommend total excision as the best therapeutic choice, individualized treatment strategy should be chosen based on the tumor stage, grade, size, number, and other factors to balance the therapeutic benefit and patient's quality of life. This study aimd to identify the risk factors for recurrence after G-NET treatment and evaluate the effectiveness of individualized treatment.

Methods

Ethical approval

This retrospective multicenter study was conducted in accordance with the 1975 *Declaration of Helsinki* and approved by the Ethics Committee of Peking Union Medical College Hospital (No. B483). The Medical Ethics Committee of Yantai Yuhuangding Hospital and Beijing Zhong-Neng-Jian Hospital approved the use of all data in the study. Written informed consent was obtained from each enrolled participant.

Study population and data collection

In total, 94 patients who had been diagnosed with well-differentiated G-NET based on biopsy or excision specimens and treated at Peking Union Medical College Hospital, Yantai Yuhuangding Hospital, and Beijing Zhong-Neng-Jian Hospital from November 2015 to September 2023 were included in this retrospective study. Patients with poorly differentiated tumor morphology, additional serious chronic illnesses, and incomplete clinical data were excluded.

The following data were collected from the patients' medical records: age, sex, clinical symptoms, laboratory data (including serum gastrin and hemoglobin levels before and after treatment etc.), endoscopic manifestations, histopathologic features (including pathologic grade and immunohistochemical markers etc.), imaging information, treatment details (including endoscopic therapy, somatostatin analog [SSA] therapy, and surgery), and outcomes (including time elapsed until the first recurrence). All patients underwent upper gastrointestinal endoscopy to assess the size, number, morphology, and location of the lesions and to confirm the existence and degree of atrophic gastritis and intestinal metaplasia. The depth of invasion was determined by endoscopic ultrasonography and pathological findings. To determine whether lymph node or distant metastases were present, computed tomography, magnetic resonance imaging, and occasionally functional imaging with somatostatin receptor scintigraphy were also performed.

Definitions of clinical stages and pathologic grades

Clinical classification of G-NET was performed according to the European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines.[7] The most prevalent classification, accounting for 75% to 80% of all G-NET, is type 1 G-NET. These tumors originate from enterochromaffin-like (ECL) cells when chronic atrophic gastritis (CAG) is present, leading to hypergastrinemia and gastric acid deficiency. Approximately 5% to 10% of G-NET are type 2 G-NET, which are characterized by hypergastrinemia and hyperacidity linked to Zollinger–Ellison syndrome and multiple endocrine neoplasia type 1 syndrome. Type 3 G-NET, which comprise 15% to 25% of G-NET, are more aggressive spontaneous tumors with normal serum gastrin and gastric acid concentrations that develop in otherwise healthy gastric mucosa.

In the present study, the G-NET were graded in accordance with the 2019 WHO Classification of Gastrointestinal Tumors (Fifth Edition) based on their mitotic number and/or Ki-67 index. Grade 1 (G1) NETs had a mitotic count of <2 per 10 high-power fields (HPFs) and/or a Ki-67 index of ≤2%. G2 NETs had a mitotic count of 2–20 per 10 HPFs and/or a Ki-67 index of 3–20% in a hotspot of at least 500 cells. G3 NETs had a mitotic count of >20 per 10 HPFs and/or a Ki-67 index of >20% in a hotspot of at least 500 cells.

Treatment strategy

Referring to Chinese expert consensus on gastroenteropancreatic NENs and ENETS Consensus Guidelines, the treatment plan for all G-NET was based on thoroughly assessing the clinical stage, histological grade, tumor location, size, number, depth of infiltration, lymph node invasion, and distant metastasis. For types 1 and 3 G-NET involving fewer than six lesions, a maximum lesion diameter of <2 cm, limitation to the mucosa and submucosa, and no lymph node or distant metastases, endoscopic resection was performed using either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). Type 1 G-NET involving six or more lesions were treated with SSAs via intramuscular injection of 20 mg octreotide acetate microspheres every 4 weeks. Type

2 G-NET and all G-NET (regardless of type) of which the maximum diameter of the lesion ≥2 cm, invaded the muscularis propria, or showed signs of local lymph node or distant metastasis were treated by surgical resection including partial gastrectomy, radical gastrectomy, and resection of the primary lesions.

Treatment response criteria

According to worldwide treatment recommendations, the response to therapy was characterized as remission (total disappearance of all clinical and radiological indications of the tumor), partial response (≥50% reduction in all measurable tumors and clinical symptoms without the development of new lesions), stable disease (<50% reduction or 25% increase in tumor size and clinical symptoms), or recurrence (development of new lesions or ≥25% increase in tumor size as well as deterioration in clinical status).

Patient follow-up

All patients were followed up through routine outpatient evaluations, examination of hospital medical records, and telephone consultations. The outpatient evaluation included several different procedures, including endoscopy, blood tests, imaging scans, and others. The length of follow-up included the time from the first diagnosis of G-NET to the most recent follow-up. Gastroscopy was performed 6–12 months after endoscopic resection, SSA therapy, and surgical treatment, and then repeated on an annual basis thereafter. The recurrence rate after treatment of G-NET is calculated, respectively, as the ratio of the number of relapses during the first, second, and third year to the number of patients who were completely followed up for one, two, and three years.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables are expressed as number with percentage, while continuous variables are expressed as median (Q_1, Q_3) or mean ± standard deviation. Continuous variables were compared using the Mann–Whitney *U* test or one-way analysis of variance (ANOVA), whereas categorical variables were compared using Pearson's chi-squared test or Fisher's exact test. To determine the risk factors for G-NET recurrence, a univariate analysis was conducted using Pearson's chi-squared test. Variables with *P* value <0.20 were chosen for subsequent multivariable logistic regression analysis. All tests were double-sided, and a *P* value of <0.05 was considered statistically significant.

Results

General characteristics

In total, 94 patients with well-differentiated G-NET were included in this analysis. As shown in Supplementary Table 1, http://links.lww.com/CM9/B907, their ages ranged from 29.0 to 77.0 years (mean, 55.2 ± 10.4 years), and they comprised 38.3% men and 61.7% women. Diagnosis of G-NET is challenging because of their diverse clinical manifestations and lack of specificity. In this study, the average time from first visit to diagnosis was 35 months; the longest diagnosis took 10 years. Among the 94 patients, most (n = 55, 58.5%) sought medical care for dyspepsia, 26 (27.7%) reported abdominal pain, 19 (20.2%) experienced abdominal distention, and 10 (10.6%) complained of heartburn. Twenty-three (24.5%) patients experienced fatigue and were found to have comorbid anemia. In 16 (17.0%) patients, the tumors were incidentally discovered during gastroscopy.

Gastroscopic manifestations and histological findings

The gastroscopic manifestations of various subtypes of G-NET differ from one another. Figure 1 illustrates the typical endoscopic presentations of the three types of G-NET. Type 1 G-NET are typically found in the fundus and body of the stomach. They appear as multiple polypoid or submucosal elevated lesions on a background of CAG. These lesions are usually confined to the mucosa or submucosa and are pathologically graded as G1 tumors [Figure 1A,B]. Type 2 G-NET can be visually identified through gastroscopy; they exhibit a rough, swollen, and blistered appearance in the fundus and body of the stomach. These tumors can be accompanied by ulcers as well as polypoid or elevated submucosal lesions [Figure 1C,D]. Endoscopy of type 3 G-NET frequently reveals singular lesions >2 cm in diameter presenting various forms such as submucosal masses, pedunculated polyps, and crater-like foci. The tumors are typically graded as G2 and infiltrate the muscularis propria to a

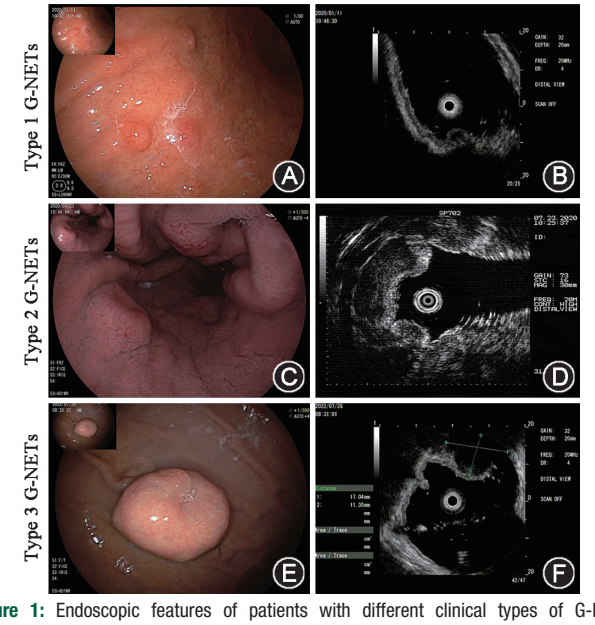

Figure 1: Endoscopic features of patients with different clinical types of G-NET. (A) Gastroscopic view of multiple polypoid lesions of 5 mm in diameter. (B) Endoscopic ultrasonography of a hypoechoic lesion limited to the submucosa in the gastric body. (C) Gastroscopy showed multiple polypoid elevations on the thick gastric body folds. (D) Endoscopic ultrasonography showed that the lesion was limited to the submucosa. (E) Endoscopic examination of a solitary lesion of 2.5 cm in diameter located in the gastric body. (F) Ultrasonographic endoscopic visualization of a lesion invading the muscularis propria. G-NET: Gastric neuroendocrine tumors.

significant extent [Figure 1E,F]. Of the 94 patients with G-NET in this study, 78 (83.0%) had type 1, 4 (4.3%) had type 2, and 12 (12.7%) had type 3. According to the 2019 WHO classification, 66 (70.2%) of all 94 cases were identified as G1 tumors, 26 (27.7%) were G2 tumors, and 2 (2.1%) were G3 tumors. Figure 2 shows the common pathological features and immunohistochemical staining of biomarkers in G-NET of all three grades. The cytoplasm of NET cells diffusely expresses chromogranin A (CgA) and synaptophysin (Syn). In the present study, immunohistochemical staining was positive for CgA in 93 (98.9%), Syn in 92 (97.9%), and CD56 in 72 (76.6%) patients [Figure 2].

Notably, CAG was not detected in all type 1 NETs in this study. Of the 78 type 1 NETs, 73 were confirmed to be associated with CAG or autoimmune atrophic gastritis through endoscopy or histology, and the remaining 5 that were unassociated with CAG may have been early-stage lesions or unsuitable biopsy sites. Similar to previous research, endoscopy confirmed the frequent incidence of multiple tumors in patients with G-NET. In the present study, 55 (58.5%) patients had single G-NET, while the remaining 39 (41.5%) had multiple lesions; 22 (23.4%) patients had >6 lesions.

Therapeutic management

Of the 63 (67.0%) patients who underwent endoscopic resection, 14 (14.9%) underwent EMR, and all of these procedures were for type 1 G-NET. Among these patients, 12 had G1 NETs and 2 had G2 NETs. In total, 49 (52.1%) patients were treated with ESD, including 42 with type 1 G-NET and 7 with type 3 G-NET. Among these patients, 34 had G1 NETs and 15 had G2 NETs. All 22 (23.4%) patients who received SSA therapy had type 1 G-NET, with 17 being G1 NETs and 5 being G2 NETs. None of the above-mentioned patients had G3 NETs. Nine (9.6%) patients underwent surgical treatment, including four patients with type 2 G-NET, five with type 3 G-NET, three with G1 NETs, four with G2 NETs, and two with G3 NETs. Among these patients, three underwent partial gastrectomy and six underwent radical gastrectomy.

Recurrence rate and clinical outcome

All 94 patients underwent regular follow-up ranging from 3 months to 93 months (median, 49 months). Of the 63 patients treated endoscopically, 14 underwent EMR and 6 developed recurrence during follow-up. Additionally, of the 49 patients who underwent ESD, 5 developed recurrence during follow-up. Complete remission was observed in 52 patients treated endoscopically, and all 11 who suffered from recurrence underwent ESD again. Finally, one of the nine patients who underwent surgical resection developed recurrence. Nine of the 22 patients who received SSA treatment achieved complete remission, 7 showed a partial response, 5 had stable disease, and 1 developed recurrence and required additional surgery. The overall recurrence rate was 13.8% (13/94 patients). Median time to first relapse was 11 months, with a range from 7 months to 42 months. Recurrence rates in the first, second, and third years after initial treatment were 8.3% (7/83), 5.8% (4/69), and 1.7% (1/58), respectively.

Table 1 listed the recurrence of G-NET in different clinicopathological conditions. Among all observed clinicopathological parameters, including age, sex, tumor size, location, number, depth of infiltration, type, grade, serum gastrin level, treatment approach, and post-treatment time, only pre-treatment gastrin level and the type of treatment showed a significant correlation with G-NET recurrence based on a univariate analysis with Pearson's chi-squared test (P = 0.018, 0.014, Table 1). Multifactorial logistic

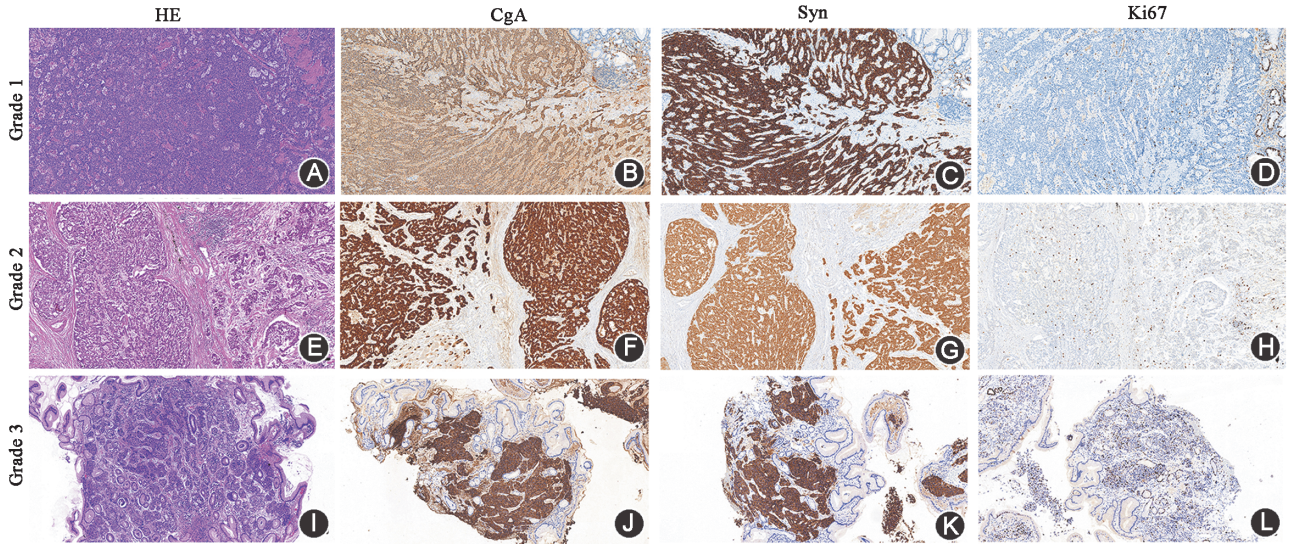

Figure 2: Pathological grading and immunohistochemical examination of biological markers of G-NET (Original magnification, ×100). Histopathological examination of G1 G-NET showed (A) a highly differentiated tumor (HE staining); (B) diffuse, strongly positive expression of CgA; (C) diffuse, strongly positive expression of Syn; and (D) a Ki-67 index of 1%. Histopathological examination of G2 G-NET showed (E) a highly differentiated tumor (HE staining); (F) diffuse, strongly positive expression of CgA; (G) diffuse, strongly positive expression of Syn; and (H) a Ki-67 index of 5%. Histopathological examination of G3 G-NET showed (I) a highly differentiated tumor (HE staining); (J) diffuse, strongly positive expression of CgA; (K) diffuse, strongly positive expression of Syn; and (L) a Ki-67 index of 30%. CgA: Chromogranin A; G-NET: Gastric neuroendocrine tumors; HE: Hematoxylin and eosin; Syn: Synaptophysin.

Table 1: Chi-squared analysis of recurrence in patients with well-differentiated G-NET.

Variables	Recurrent group ($n = 13$)	Non-recurrent group ($n = 81$)	χ^2 value	*P* value
Age			<0.001	>0.999
<50 years	2	14		
≥50 years	11	67		
Gender			0.087	0.769
Male	4	32		
Female	9	49		
Maximal tumor size			0.018	0.892
<10 mm	8	55		
≥10 mm	5	26		
Number of gastric lesions			1.185	0.276
<6	12	60		
≥6	1	21		
Location of primary*			–	>0.999
Body	9	58		
Fundus	1	7		
Antrum	1	5		
Body + fundus	2	11		
Clinical classification*			–	0.657
Type 1	11	67		
Type 2	1	3		
Type 3	1	11		
Depth of invasion			–	0.533
Mucosa/submucosa	12	77		
Muscularis propria	1	4		
Grade*			–	0.269
Grade 1	8	58		
Grade 2	4	22		
Grade 3	1	1		
Pre-treatment Serum Gastrin			5.603	0.018
<1000 pg/mL	2	41		
≥1000 pg/mL	11	40		
Treatment*			–	0.014
EMR	6	8		
ESD	5	44		
SSA	1	21		
Surgical resection	1	8		
Post-treatment time*			–	0.286
First year	7	76		
Second year	4	65		
Third year	1	57		

*P values obtained using Fisher's exact test. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; G-NET: Gastric neuroendocrine tumors; SSA: Somatostatin analog; –: None.

regression analysis further confirmed that pre-treatment gastrin level and treatment method were both independent risk factors for G-NET recurrence ($P = 0.005$ and 0.017 repectively, Table 2). Additionally, this analysis revealed a statistically significant difference between the ESD and EMR groups ($P = 0.010$, Table 2) as well as between the SSA and EMR groups ($P = 0.006$, Table 2).

Upon examining the effects of long-term SSA treatment, a significant trend toward decreasing serum gastrin levels was observed before and after treatment, with a decrease from 1081.0 (571.5, 2472.8) pg/mL to 461.5 (255.3, 795.0) pg/mL (Mann–Whitney U test, $Z = -3.521$, $P < 0.001$) [Figure 3A]. The one-way ANOVA results showed that serum gastrin levels were significantly lower at different time points after treatment compared to those before treatment ($F = 9.038$, $P < 0.001$). Additional Dunnett's T3 test revealed that such significant reduction in serum gastrin was observed from the second month (661 ± 267 pg/mL, $P = 0.04$) [Figure 3B]. However, there was no significant difference in serum gastrin levels among different time points after treatment.

Table 2: Multifactorial logistic regression analysis of recurrence in patients with well-differentiated G-NET.

Variables	β-value	Standard error	Wald χ^2 value	OR	95% CI	*P* value
Pre-treatment serum gastrin	0.001	<0.001	8.058	1.001	1.000–1.002	0.005
Treatment			10.197			0.017
EMR (ref)						
ESD	–2.031	0.788	6.648	0.131	0.028–0.614	0.010
SSA	–3.644	1.326	7.544	0.026	0.002–0.352	0.006
Surgical resection	–1.979	1.329	2.217	0.138	0.010–1.870	0.137

CI: Confidence interval; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; G-NET: Gastric neuroendocrine tumors; OR: Odds ratio; SSA: Somatostatin analog.

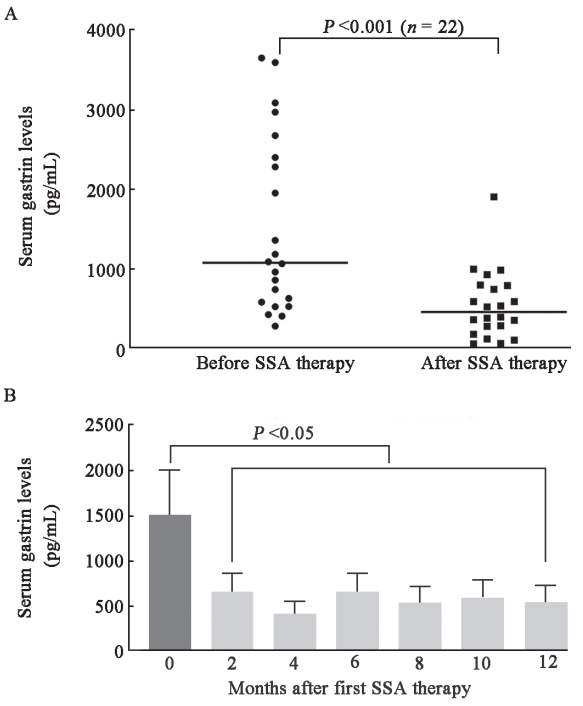

Figure 3: Monitoring of serum gastrin levels during SSA treatment in G-NET patients. (A) Changes in serum gastrin levels before and after SSA therapy in patients with G-NET. (B) Serum gastrin levels in G-NET patients treated with continuous SSA therapy for 12 months. G-NET: Gastric neuroendocrine tumors; SSA: Somatostatin analogue.

Metastases were present in only three (3.2%) patients, all of whom had them in the locoregional lymph nodes, and two of whom also had them in the liver. Two of these patients had G2 tumors and one had G3. Therefore, a statistical analysis could not be performed to predict metastasis and its impact on the prognosis of type 1 G-NEN. One patient who had type 3 G-NET (WHO grade 3) with liver and lymph node metastases died, resulting in a survival rate of 98.9%.

Discussion

G-NEN are rare tumors with variable biology that originate from various neuroendocrine cells within the stomach, and diagnosis is often delayed.[1] The annual incidence of G-NEN has been progressively rising in recent years.[2] The present study focused on well-differentiated G-NET, which account for 80% of all G-NEN. Compared with gastric neuroendocrine carcinoma, the incidence of G-NET increased more rapidly, with a >16-fold rise to 4.978 per 1,000,000 population.[4]

According to a study by Hu *et al*[4] that involved 246 patients with G-NEN at 8 tertiary hospitals in Jiangsu province, the prevalence was somewhat higher in women than in men. Additionally, the median age at diagnosis for patients with G-NET (55 years) was substantially lower than that of patients with gastric neuroendocrine carcinoma (66 years). Similar to that study, the number of G-NET in the present study was higher in women than in men, and the mean age at diagnosis was 55.2 ± 10.4 years (range, 29–77 years).

In this study, patients with G-NET displayed various clinical symptoms such as abdominal pain (26/94, 27.7%), abdominal distension (19/94, 20.2%), heartburn (10/94, 10.6%), anemia-induced malaise (23/94, 24.5%), and complete absence of symptoms (16/94, 17.0%). Among all 94 patients, 65 (69.1%) had either single or multiple nodules or polypoid elevations in the gastric body and fundus detected through endoscopy, and some of the tumors were difficult to distinguish from glandular polyps. In some patients, early diagnosis and therapy were difficult because of the lack of specificity of clinical symptoms and endoscopic findings. The average time until diagnosis was 35 months, with the longest diagnosis time extending to 10 years. Endoscopists should concentrate on endoscopic direct observation of the tumor and background gastric mucosa and emphasize pathological biopsy in clinical practice to prevent missed diagnoses.

Accurate clinical typing and grading is the cornerstone of individualized treatment for G-NET. Type 1 G-NET are the most prevalent subtype of G-NET (75–80%) with typically G1 tumors that progress slowly, rarely metastasize (metastasis rate of 1–3%), and have a favorable prognosis with a 5-year survival rate of up to 96%.[11] However, they exhibit a high recurrence rate, with some studies suggesting that the recurrence rate can reach 52%.[10] In this study, 78 (83.0%) patients had type 1 G-NET, of which 62 were classified as G1, consistent with the outcomes of prior investigations. Type 2 G-NET are prevalent in patients with gastrinomas originating from the pancreas and duodenum, with 20–30% occurring in patients with multiple endocrine neoplasia type 1. The grade of most tumors is G1, and the metastasis rate ranges from 10% to 30%.[12] After surgical treatment, the survival rate of patients without metastasis can exceed

80% over a 15-year period.[13] In this study, four patients were diagnosed with type 2 G-NET, of whom three had gastrinomas and one had multiple endocrine neoplasia type 1. All four patients underwent surgical treatment. After a median follow-up of 39 months, one recurrence was re-operated, and no metastasis was detected. The survival rate was 100%. With pathological grades of G2 and G3 and an unknown pathogenesis, type 3 G-NET have a poor prognosis. Studies have demonstrated a 5-year survival rate of <50%, with 29.9% of surviving patients having localized metastasis and only 10.0% having distant metastasis.[14,15] Twelve patients with type 3 G-NET were included in the present study. The patients predominantly had G2 (9/12, 75.0%) and G3 (2/12, 13.3%) tumors, and three (25.0%) of them had lymph node or liver metastases at the time of diagnosis. One patient died after 24 months of follow-up.

Pathological evaluation with immunohistochemical analysis of specific biomarkers is the definitive diagnostic method for G-NET and identifies tumor grading. Figure 2 shows the typical pathological changes and immunohistochemical staining of G-NET of different grades. Essential tests for the diagnosis of NETs include immunohistochemical staining for the biomarkers CgA, Syn, and CD56. CgA is more specific, whereas Syn and CD56 are more sensitive but slightly less specific because they are expressed not only in neuroendocrine cells.[16] The present study showed a 98.9% positivity rate for CgA, 97.9% for Syn, and 76.6% for CD56. The combination of these markers should be utilized to enhance diagnostic accuracy.

Management options for highly differentiated G-NET include endoscopic surveillance, endoscopic resection, administration of SSAs, and surgical intervention. Whether endoscopic surveillance or endoscopic excision is the best choice for treating type 1 G-NET of 1–2 cm in diameter is debatable. According to the Chinese expert consensus on gastroenteropancreatic NENs (2022 edition), endoscopic resection or follow-up observation is possible for multiple tumors of <1 cm.[17] For G-NET of ≥1 cm, endoscopic ultrasound should be performed to determine whether surgical or endoscopic resection is necessary based on the depth of infiltration and presence of lymph node metastasis. The ENETS suggests that type 1 G-NEN with lesions <1 cm should be monitored every 1–2 years. For G-NEN with a diameter of 1–2 cm, the ENETS recommends endoscopic resection for patients with lesions that do not invade muscularis propria, whereas the National Comprehensive Cancer Network (NCCN) guideline proposes that either endoscopic surveillance or endoscopy is acceptable.[7,18] In a recent study by Chin *et al*,[19] the risk of disease progression during monitoring was 29.5%, showing that basic surveillance may not be secure in these patients.

In some cases of scattered multiple type 1 G-NET, endoscopic resection may not effectively remove all the lesions, leading to a high incidence of intragastric recurrence. SSA therapy can be considered as a treatment option for these patients.[17] According to a meta-study involving 117 patients, SSAs had an excellent response rate after 12 months on therapy (i.e., a cumulative complete response rate of 84.5% when considering the six prospective studies) in selected patients who could not be safely managed by endoscopic follow-up or resection.[20] In the present study, 22 patients were treated with SSAs; among them, 16 achieved varying degrees of remission, 5 had stable illness without progression, and only 1 suffered from recurrence. Following a median follow-up of 29 months, no adverse reactions or significant side effects were detected, suggesting that SSAs are both safe and efficient in the treatment of G-NEN.

The management of type 2 G-NET involves surgical removal of the G-NET as well as the treatment of gastrinomas.[21] If the gastrinoma is operable, a logical surgical approach should be selected according to its location and size. Total gastrectomy is another option if the location of the main tumor cannot be determined.[22] In the presence of liver metastases, SSA therapy represents the preferred primary therapy.[23] The management of type 3 G-NEN is contentious. Previous studies have concluded that type 3 G-NET are highly aggressive and require gastrectomy combined with lymph node dissection regardless of tumor size.[24] However, a recent study by Hirasawa *et al*[25] showed that endoscopic resection is appropriate for type 3 G-NEN that have a diameter of <10 mm and are confined to the mucosa or submucosa because only 1 of the 48 patients presented with recurrence.

Considering the treatment effect and patients' quality of life, the above-mentioned individualized treatment strategy was selected for this investigation. The results showed a lower overall recurrence rate of 13.8% (13/94 patients) than in other comparable trials. These findings suggest that the personalized treatment approach utilized in this study may be effective for reducing the recurrence rate of G-NET. Post-treatment recurrence rates were significantly different ($P = 0.014$) among four treatments, and EMR had a significant higher risk of recurrence (6/14, 42.9%) than ESD (5/49, 10.2%) and SSA therapy (1/22, 4.5%). Most G-NET have a tendency to invade the submucosal layer. Consequently, conventional EMR is often inadequate for achieving sufficient resection depth and complete tumor removal. Compared to EMR, ESD allows complete resection of both horizontal and vertical margins in larger lesion. Positive vertical margins were observed in 66% of EMR-resected G-NET according to Sato's study, while ESD did not yield positive horizontal or vertical margins.[26] We believe that these reasons contributed to the significantly lower recurrence rate of G-NET after ESD treatment than EMR in this study.

Among the four kinds of treatment methods, SSA treatment exhibited the lowest recurrence rate (1/22, 4.5%, Fisher's exact test, $P = 0.014$), indicating that SSA therapy may be an effective measure for reducing the likelihood of recurrence of type 1 G-NET with more than six intragastric lesions. SSA can reduce the secretion of gastrin by binding to somatostatin receptors 2 (SSTR2) and SSTR5 on ECL cells. This reduces the level of gastrin in the blood and its nutritive effect on ECL cells, inhibiting their proliferation and preventing the occurrence of G-NET. Moreover, SSA has antitumor proliferative effects. On one

hand, it directly blocks the cell cycle and promotes apoptosis by binding to SSTR; on the other hand, it indirectly inhibits tumor growth by inhibiting vascular endothelial growth factor expression and reducing tumor blood vessel formation. Given the significant involvement of hypergastrinemia in the pathogenesis of most G-NET, G-NET can be considered as a localized clinical manifestation of a systemic disease. Therefore, systemic therapy may be a more effective approach than localized therapy alone. A prospective study by Massironi *et al*[27] showed significant reduction in gastrin and CgA and disappearance of tumors in 25 patients with recurrent G-NET after treatment of median duration of 12 months. The present study showed similar results, revealing a decline in serum gastrin levels with a significant decrease from the second month onward. However, it should be noted that 4 out of 12 patients experienced relapse after a median time of 19.5 months after discontinuation of SSA according to Massironi's study.[27] Therefore, well-designed prospective studies could be conducted in the future to further clarify the treatment regimen of SSA and the interval between treatments.

In addition to the choice of therapeutic strategy, this study also found a significant correlation between pretreatment gastrin levels in G-NET and the recurrence of lesions after treatment, which is consistent with the findings of Daskalakis *et al*.[9] Although the predictive value of serum gastrin levels in the recurrence of G-NET has not been fully established, we recommend that future clinical work emphasize monitoring serum gastrin levels in patients with G-NET and intensifying endoscopic follow-up of patients with hypergastrinemia due to the key role of hypergastrinemia in the pathogenesis of G-NET.

There are some limitations in this study. First, it is a retrospective study and therefore subject to some information bias in the data of the included patients. Second, as G-NET are rare diseases, many hospitals do not perform all four treatments, including EMR, ESD, SSA, and surgery. Therefore, this study screened three hospitals that have carried out all four treatments mentioned above for G-NET and have complete clinical data, which made the sample size for inclusion relatively small. Furthermore, this study had a limited number of G2 and G3 G-NET, a short observation period in some patients, and a relatively small number of recurrences. In the future, it is proposed to conduct a large-scale, multicenter prospective study to expand the number of study hospitals and cases, hoping that this will provide a foundation for further standardization of the treatment of G-NET.

In summary, well-differentiated G-NET have a good overall prognosis and a low incidence of metastasis and mortality but a high likelihood of lesion recurrence after treatment. This study revealed that pretreatment serum gastrin levels and choice of treatment strategy were significantly correlated with recurrence rate of G-NET after treatment. Furthermore, these data stress the importance of individualized treatment plans for patients with G-NET based on factors such as the tumor type, grade, number of lesions, size, and metastasis. Such personalized plans may decrease disease recurrence rates. For type 1 G-NET with more than six lesions, long-term SSA therapy may be a safe and effective treatment option. It also significantly reduces the likelihood of recurrence after treatment.

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Conflicts of interest

None.

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