

# Clinicopathological Features and Prognosis of Gastric Neuroendocrine Neoplasms

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## Research

**Keywords:** stomach, neuroendocrine neoplasm, classification, pathology, prognosis

**Posted Date:** July 6th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-39979/v1>

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# Abstract

**Purpose:** We performed a retrospective study to investigate the relationship between clinicopathological features and prognosis of G-NEN.

**Methods:** Clinicopathological features and follow-up data of 67 patients with G-NEN treated at Shandong Provincial Hospital affiliated of Shandong University were analyzed retrospectively.

**Results:** This whole cohort included 53 males and 14 females, with a mean age of  $59.37 \pm 9.80$  years. The clinical symptoms and the primary tumor site were not specific. Neuroendocrine tumor, neuroendocrine carcinoma, and mixed neuroendocrine–non-neuroendocrine neoplasm accounted for 14.93%, 59.70%, and 25.37%, respectively. TNM stages I–IV: 6, 6, 49, 4, respectively. All patients underwent surgically treated. Forty-five patients underwent laparoscopic surgery, and twenty-two patients received an open approach. The median survival time was 36 months in all patients. The overall survival rate for the entire cohort was 68.1 %, 44.7 %, and 34.5% at 1, 3, and 5 years, respectively. Logistic regression analysis revealed that the invasive depth of tumors was predictors for metastasis. The univariate analysis confirmed that smoking, T stage, distant metastasis, and surgical method were related to survival. COX regression analysis showed that the T stage (HR=4.817, 95%CI: 1.021-22.729, P=0.047) was an independent risk factor for evaluating the prognosis of patients with G-NEN.

**Conclusions:** G-NEN is a kind of rare tumors that can occur at any part of the stomach. The clinical features are not specific. The tumor invasive depth related to tumor metastasis. The prognosis is associated with smoking, T stage, distant metastasis, and surgical method. Of them, T stage is an independent prognostic factor for G-NEN patients. But larger studies are needed in the future.

## Introduction

Neuroendocrine neoplasm (NEN) is a group of heterogeneous neoplasms that originated from peptidergic neurons and neuroendocrine cells.[1] It occurs in many organs and tissues of the body, such as the gastrointestinal tract, pancreas, bronchus, lung, breast, pituitary gland, etc. and different sites of NEN have different clinical characteristics. It is most commonly in the digestive system. The incidence of gastric neuroendocrine (G-NEN) is higher in gastrointestinal and pancreatic neuroendocrine neoplasms(GEP-NEN). However, G-NEN is Still considered as a rare disease with an incidence of 0.3 per 100000 each year [2]. The clinicopathological characteristics of G-NEN are different in patients over the world. A number of studies have generally grouped all neuroendocrine tumors of the digestive system into one[3–5], but studies focus on G-NEN alone Accounted for very little. Therefore, we retrospectively collected the clinicopathological data and follow-up data of patients with a gastric neuroendocrine tumor in a Chinese hospital in this study, and we conducted a detailed analysis aiming to explore the clinicopathological characteristics of patients with G-NEN and the factors related to survival, which might provide new clues for the research of this sort of tumors.

## Methods

### Patients selection

We retrospectively reported and analyzed clinical data from patients diagnosed with G-NEN at Shandong Provincial Hospital affiliated of Shandong University between January 2011 and December 2019. The inclusion criteria were as follows: (1) Patients were pathologically diagnosed as primary G-NEN by the pathologists at our institution. (2) The pathological diagnosis of the G-NENs contains the maximum tumor diameter, invasion depth, WHO classification, immunohistochemistry, local lymph node metastasis, ki-67% index, and Immunohistochemical markers of G-NEN. The exclusion criteria were as follows: (1) Patients also had other types of tumors except for the G-NEN. (2) Patients whose clinical features and pathological diagnosis were incomplete. Finally, a total of 67 cases of G-NEN patients were included in this study.

### Pathological stage and classification

As for the TNM stage and pathological classification diagnostic criteria, we adopted the WHO's new version classification of digestive system tumors[6]. Based on it, the G-NEN can be divided into four stages according to the depth of invasion, lymph node invasion, and distant metastasis. On the other hand, it can be divided into three categories: neuroendocrine tumor (NET) that contains NET G1, NET G2 and NET G3, neuroendocrine carcinoma (NEC), and mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN).

#### Follow-up

We mainly conducted telephone return visits, in-patient review, and outpatient follow-up, and the follow-up time was from the diagnosis of the disease to the death of the patient or the last follow-up time.

### Data collection and statistical analysis

The following information was reported and analyzed: clinical characteristics (gender, age, history, the primary location of tumors, clinical symptoms), tumor's histopathological features (size, histopathology of the primary tumor, grading, metastases), method of treatments (open surgery or laparoscopic surgery), and follow-up (whether to conduct postoperative adjuvant therapy, date of death and cause of death).

All statistical analyses were performed using SPSS 22.0 for Windows (IBM Corp. Released 2013, Armonk, NY: IBM Corp). Normally distributed continuous variables were expressed as mean and standard deviation. Differences in categorical variables were compared with the chi-square test or Fisher's exact test if necessary. Overall survival (OS) was defined as the time from diagnosis to death or, in living patients, the time to last follow-up. Survival curves were drawn according to the Kaplan-Meier method, and differences between subgroups were assessed with the Log-rank test. Multivariate analysis of independent prognostic factors was performed using a Cox proportional hazards model. P-values < 0.05 were considered statistically significant.

## Results

### Clinical and demographic features

After reviewing the medical records, 67 patients were enrolled in the cohort. Among all the included G-NEN patients diagnosed in Shandong Provincial Hospital Affiliated of Shandong University between January 2010 and December 2019, 53 (79.10%) were men, and 14 (20.90%) were women; the M/F sex ratio was 3.79:1. Ages ranged from 39 to 79 years old. The mean age of G-NEN patients is  $59.37 \pm 9.80$  years, and the mean age in male patients was of  $61.23 \pm 8.89$  years, compared to  $52.36 \pm 10.03$  years in female patients. There was gender difference in primary tumor site, as listed in Table 1, the most common primary tumor site was the gastric body (n = 23, 34.33%), followed by the gastric antrum (n = 21, 31.34%), cardia (n = 13, 19.40%), fundus of stomach (n = 8, 11.94%), pylorus (n = 1, 1.49%). Particularly, there is one case where the tumor occupies the fundus of the stomach and the stomach body and the cardia (n = 1, 1.49%). The most frequent initial clinical symptoms was abdominal pain (23/67, 34.33%), followed by abdominal distention (16/67, 23.88%), Indescribable upper abdominal discomfort (11/67, 16.42%), dysphagia (3/67, 4.48%), bleeding (3/67, 4.48%), heartburn (1/67, 1.49%), emaciation (1/67, 1.49%) and hiccup (1/67, 1.49%), eight (11.94%) cases were found during routine physical examination. The detailed demographic and clinical characteristics are shown in Table 1.

Table 1  
Population and clinical characteristics of the study

	Male	Female	Total [N(%)]
Numbers(N) (%)	53(79.10%)	14(20.90%)	67(100.00%)
Age(years)	61.23 ± 8.89	52.36 ± 10.03	
ASA score			67(100.00%)
1	39	9	48(71.64%)
2	14	5	19(28.36%)
Smoke			67(100.00%)
no	20	14	34(50.75%)
yes	33	0	33(49.25%)
Alcohol			67(100.00%)
no	27	14	41(61.19%)
yes	26	0	26(38.81%)
Original clinical symptoms			67(100.00%)
Abdominal pain	18	5	23(34.33%)
ventosity	13	3	16(23.88%)
epigastric sensory	8	2	10(14.93%)
found during routine physical examination	4	4	8(11.94%)
swallowing	3	0	3(4.48%)
Digestive tract bleeding	3	0	3(4.48%)
emaciation	1	0	1(1.49%)
heartburn	1	0	1(1.49%)
hiccup	1	0	1(1.49%)
anorexia	1	0	1(1.49%)
Primary site of tumor			67(100.00%)
cardia	12	1	13(19.40%)
fundus	6	2	8(11.94%)
body	16	7	23(34.33%)

	Male	Female	Total [N(%)]
antrum	17	4	21(31.34%)
pylorus	1	0	1(1.49%)
other <sup>a</sup>	1	0	1(1.49%)
Operation			67(100.00%)
curative resection	48	11	59(88.06%)
palliative resection	5	3	8(11.94%)
surgery method			67(100.00%)
open surgery	15	7	22(32.84%)
Laparoscopic surgery	38	7	45(67.16%)
Adjuvant chemotherapy <sup>b</sup>			N = 56(100.00%)
No	21	8	29(51.79%)
Yes	23	4	27(48.21%)

1. a. tumor occupied more than one site

2. b. This data was derived from follow-up information in which 11 patients were lost to follow-up. So, the total is 56

## Pathological characteristics

The histopathologic characteristics (size, TNM stage, WHO classification) of the 67 patients of G-NEN are given in Table 2. According to the pathology results of the 67 tumors, the mean size (maximum tumor diameter) of the tumors was  $5.00 \pm 2.72$  cm.

According to the TNM staging system, T staging can be used to describe the depth of tumor infiltration. In our cohort, T1, T2, T3 and T4 accounted for 14.93%(n = 10), 20.90%(n = 14), 4.48%(n = 4) and 59.70%(n = 40) respectively. At diagnosis, Lymph node invasion occurred in 70.77% (n = 46) in 65 patients (two cases didn't report the lymph node invasion because they had undergone a partial removal of the tumor), and the number of positive lymph node range from 1–31, with a mean of  $6.02 \pm 5.77$ . Metastatic occurred in 5.97% (n = 4) in 67 patients when they were diagnosed with G-NEN, where all four sites of distant metastases were the liver. TNM stages in the 65 evaluable cases were as follows: Stage I in 6 patients, stage II in 6 patients, stage III in 49 patients, and stage IV in 4 patients. (Table 3)

Most reports did not present a mitotic ratio. According to the latest classification criteria, We rechecked the pathological classification based on the degree of differentiation and the Ki-67% index. It was found that 11.94% of tumors were NET G1, 2.99% were NET G2, 59.70% were NEC, and 25.37% were MiNEN.

What's special, one patient had multiple G-NEN where in addition to the largest tumor, there were ten other tumors with a diameter of 0.3–1.2 cm that invaded the submucosa. Another special patient had a gastrointestinal stromal tumor (GIST) in the serous surface of the resected specimen with a diameter of 1.2 cm except his G-NEN. The risk assessment of tumor progression was deficient.

Univariate Logistic analysis showed that only the tumor infiltration depth ( $p \leq 0.05$ ) was associated with tumor metastasis (Table 3). So, Multivariate analysis wasn't taken.

Table 2  
Pathological characteristics of G-NEN in the study

	Upper (cardia and fundus)	Middle (gastric body)	Lower (antrum and pylorus)	Other (tumor occupied more than 1 site)	Total(%)
	n = 21	n = 23	n = 22	n = 1	
Tumor size					N = 67(100%)
≤2 cm	0	6	0	0	6(8.96%)
2 ~ 4 cm	2	4	10	0	16(23.88%)
≥ 4 cm	19	13	12	1	45(67.16%)
T Stage					N = 67(100%)
T1	1	6	3	0	10(14.93%)
T2	5	3	6	0	14(20.90%)
T3	1	2	0	0	3(4.48%)
T4	14	12	13	1	40(59.70%)
N Stage					N = 65(100%)*
N0	4	12	3	0	19(29.23%)
N1	17	10	18	1	46(70.77%)
M Stage					N = 67(100%)
M0	21	21	20	1	63(94.03%)
M1	0	2	2	0	4(5.97%)
TNM stage					N = 65(100%)
I	1	5	0	0	6(9.23%)
II	0	3	3	0	6(9.23%)
III	20	12	16	1	49(75.38%)
IV	0	2	2	0	4(6.15%)
WHO classification					N = 67(100%)

	Upper (cardia and fundus)	Middle (gastric body)	Lower (antrum and pylorus)	Other (tumor occupied more than 1 site)	Total(%)
NET G1	2	4	2	0	8(11.94%)
NET G2	0	2	0	0	2(2.99%)
NEC	14	12	13	1	40(59.70%)
MiNEN	5	5	7	0	17(25.37%)

Table 3  
univariate analysis of metastasis in G-NEN patients

Prognostic factors	Number	non-metastatic	metastatic	$\chi^2$	P-value
All patients	56	36	20		
Age (years)				1.171	0.279
≤ 60	25	18	7		
>60	31	18	13		
Gender				0.285	0.593
Male	44	27	17		
Female	12	9	3		
Smoke				0.648	0.421
no	32	22	10		
yes	24	14	10		
Alcohol				0.512	0.474
no	37	25	12		
yes	19	11	8		
ASA score				0.728	0.394
1	38	23	15		
2	18	13	5		
Primary tumor location				3.036	0.219
Upper Stomach	19	11	8		
Middle Stomach	19	15	4		
Lower Stomach	17	9	8		
Maximum tumor diameter				0.160	0.690
≤ 5 cm	30	20	10		
> 5 cm	26	16	10		
T stage				4.496	0.034*
T1 + T2	20	17	3		
T3 + T4	36	19	17		

Prognostic factors	Number	non-metastatic	metastatic	$\chi^2$	P-value
Lymph node metastasis				0.728	0.394
no	18	13	5		
yes	38	23	15		
Neurovascular invasion				0.63	0.427
no	40	27	13		
yes	16	9	7		
MiNEN or not				1.070	0.301
Not MiNEN	41	28	13		
MiNEN	15	8	7		
Surgical method				0.728	0.394
Open surgery	18	13	5		
Laparoscopic surgery	38	23	15		
Operation				0.000	1.000
curative resection	46	30	16		
palliative resection	10	6	4		
Adjuvant chemotherapy				0.574	0.449
no	29	20	9		
yes	27	16	11		

## Medical therapy

All the patients underwent an operation with curative intent or palliation; Among them, 53 patients underwent the standard radical gastrectomy. In two cases, local resection was performed because the tumor had grown outside the serous membrane. (Unfortunately, these two patients were lost to follow-up, so their survival status is unknown. Twelve patients underwent palliative gastrectomy because of tumor invasion or metastasis.) In terms of surgical methods, 45 patients underwent minimally invasive laparoscopic surgery, 22 patients received the open approach; In particular, one patient underwent concurrent colectomy due to tumor invasion of the right transverse colon. According to the follow-up results of 56 patients, 27 patients received adjuvant chemotherapy after surgery, with cisplatin combined with etoposide as the primary regimen.

## Follow-up

56 out of 67 patients received long-term follow up with a median duration of 36.00 months (range 1–115 months), with the 95% Confidence Interval of 13.10 months to 58.90 months. At the last follow-up, 25 patients had died from their tumor-related complications (tumor distant metastatic in 16 patients, tumor recurrence in primary site in 5 patients, cachexia-related death in 3 patients, anastomotic leakage in 1 patient). Of the 16 patients who died of metastases, one had metastases at diagnosis, and the 15 patients had new metastases after surgery.

## **Survival time and prognostic factors**

The overall survival rate for the entire cohort was 68.1%, 44.7%, and 34.5% at 1, 3, and 5 years, respectively. An analysis was performed on patients' age, gender, smoke and drink, anesthesia score (ASA score), method of surgery, primary tumor site, maximum tumor diameter, TNM stage, pathological classification to identify possible prognostic factors for overall survival. We can see from the univariate analysis, which confirmed that smoking, T stage, distant metastasis, and surgical method were related to survival. However, age, sex, primary tumor site, maximum tumor diameter, drink alcohol, and anesthesia score have no significant correlation with the overall survival. The mean survival time and statistic data were provided in Table 3. Survival curves were displayed in Fig. 1 (A-E). Further Cox regression analysis showed that tumor invasion depth (HR = 4.817, 95%CI: 1.021–22.729, P = 0.047) was an independent risk factor for evaluating the prognosis of patients with G-NEN.

Table 4  
Survival time and related prognosis factors

Prognostic factors	Number	Mean survival time (months)	95% Confidence interval	$\chi^2$	P-value
All patients	56	52.88	(37.74–68.02)		
Age (years)				0.514	0.473
≤ 60	25	56.17	(32.80-79.55)		
≥60	31	48.28	(29.54–67.01)		
Gender				0.452	0.501
Male	44	49.33	(32.76–65.89)		
Female	12	64.44	(33.57–95.31)		
Smoke				9.716	0.002*
no	32	72.11	(52.91–91.30)		
yes	24	19.03	(12.69–25.36)		
Alcohol				1.315	0.251
no	37	61.58	(41.11–82.05)		
yes	19	40.17	(20.80-59.55)		
ASA score				0.604	0.437
1	38	52.35	(35.10-69.61)		
2	18	45.19	(20.09–70.28)		
Family history				0.254	0.6142
no	53	53.24	(37.541–68.936)		
yes	3	28	(0-57.610)		
Primary tumor location				3.628	0.163
Upper Stomach	19	39.78	(20.32–59.25)		
Middle Stomach	19	79.36	(52.75-105.98)		
Lower Stomach	17	35.94	(23.04–48.84)		
Maximum tumor diameter				3.40	0.065
≤ 5 cm	30	63.75	(42.46–85.03)		

Prognostic factors	Number	Mean survival time (months)	95% Confidence interval	$\chi^2$	P-value
> 5 cm	26	39.46	(20.85–58.07)		
T stage				10.576	0.001*
T1 + T2	20	99.44	(79.30-119.59)		
T3 + T4	36	34.79	(21.68–47.90)		
Lymph node metastasis				0.16	0.689
no	18	54.53	(37.59–71.47)		
yes	38	28.62	(13.92–43.31)		
Distant metastasis				10.919	0.001*
no	36	77.28	(57.23–97.30)		
yes	20	23.16	(16.16–30.17)		
Neurovascular invasion				0.160	0.689
no	40	54.533	37.595–71.471		
yes	16	28.616	13.917–43.315		
MiNEN or not				0.091	0.763
Not MiNEN	41	55.66	(37.43–73.89)		
MiNEN	15	44.55	(21.28–67.83)		
Surgical method				4.434	0.035*
Open surgery	18	27.46	(17.65–37.26)		
Laparoscopic surgery	38	71.14	(49.13–93.14)		
Operation				0.208	0.648
curative resection	46	54.51	(37.89–71.14)		
palliative resection	10	28.31	(12.50-44.11)		
Adjuvant chemotherapy				0.361	0.548
no	29	50.17	(31.04–69.28)		
yes	27	49.77	(28.04–71.51)		

A. Overall survival in all included patients B. Overall survival by smoking or not C. Overall survival by T staging. D. Overall survival by distant E. Overall survival by surgery method

Table 5  
Prognosis factors of survival according to COX proportional hazards model

Factors	Wald	P-value	HR	95.0% CI
smoke	1.886	0.170	1.917	0.757–4.854
Distant metastasis	2.360	0.125	2.052	0.820–5.133
T staging	3.944	0.047*	4.817	1.021–22.729
Method of surgery	2.014	0.156	1.957	0.774–4.947

## Discussion

According to the population-based study using nationally representative data from the Surveillance, Epidemiology, and End Results (SEER) program, the incidence, and prevalence of GEP-NEN are steadily rising, particularly in the small intestine, followed by rectum, appendix, colon, and stomach[7, 8]. A 12-year study from Lebanon's single-center Institute showed that G-NEN accounted for about 18%, second only to pancreatic neuroendocrine tumors[9]. With the widespread use of endoscopy and the increasing awareness among clinicians and pathologists, gastric neuroendocrine neoplasms (G-NEN) are being increasingly focused in recent years. In this study, 67 cases of G-NEN were systematically analyzed further to explore the clinicopathological features and prognostic factors of G-NEN.

In our study, the average age of all patients is 50.00 years, and the male-to-female ratio was 3.79:1. But in a large South American study[3], there were more women(61.9%) with G-NEN than men(38.1%), which may be explained with sample size and race. We can see that the effect of gender and ages on tumor metastasis and survival was not significant from our study. Among all the 67 patients, we recorded the history of smoking and drinking of patients. At the same time, anesthesiologists recorded anesthesia scores to assess their tolerance to the surgery because all patients had undergone surgery. In general, the higher the anesthesia score, the more complications the patient has. We can see from the Table 1 that patients older than 60 years of age, male patients, those with a history of smoking or drinking alcohol, and those with higher anesthesia scores had lower survival time. But with the Kaplan-Meier method, we concluded that only smoking was a risk factor for survival in patients with G-NEN. In a systematic review and meta-analysis of NEN, it was considered that smoking was a potential risk factor for G-NEN[10]. While alcohol consumption and higher ASA score had no apparent effect on prognosis, all clinical

features were not associated with tumor metastasis. In our cohort, family history is defined as the occurrence of cancer in an immediate family member. As shown in Table 4, three patients had a family history of cancer, and there was no significant correlation between family history and prognosis.

G-NEN can be divided into a functional one and non-functional one according to whether the tumor has specific hormone secretion and related clinical characteristics[11]. In this study, non-functional accounted for the majority of the patients. As we can see that the clinical feature of G-NEN above, in our research, the primary clinical manifestations of all the included patients were not specific with the most frequent initial clinical symptoms of abdominal pain (23/67, 34.33%), which is definitely a challenge for the diagnosis of the disease. We also found that G-NEN can occur any portion in the stomach, and there was no significant difference at the tumor site. In some cases, tumors were so large or so numerous that they could occupy multiple parts of the stomach.

G-NEN can be classified into three types based on clinical features. Type I G-NEN relates to autoimmune chronic atrophic gastritis. Type II is caused by gastrinomas, which is known as Zollinger-Ellison syndrome. Type III consists of a sporadic lesion and has the most significant potential to generate metastasis, which has characteristics similar to gastric adenocarcinoma [12]. In our study, due to the imperfect gastrin examination, the clinical type was not performed. The nomenclature and classification criteria of G-NEN were consistent with those of gastrointestinal and pancreatic neuroendocrine tumors (GEP-NEN). To standardize the stratification and management procedures, in 2010, GEP-NEN was divided into G1, G2, and G3 based on a ki-67 index and mitotic index, among which G1 and G2 tumors were called neuroendocrine tumors (NET) and G3 tumors were called neuroendocrine cancers (NEC). If NEC tissues are mixed with adenocarcinoma, and when the ratio of both is above 30%, it is called mixed adenocarcinoma (MANEC). In 2019, the new version updated the classification of NEN[6], NEN was divided into two categories: highly differentiated NET and poorly differentiated NEC. NET includes G1, G2, and G3 levels, where G1 and G2 levels are defined in the same way as in 2010, while NET G3 levels refer to NEN, where the ki-67 index is above 20%. However, morphological characteristics still retain highly differentiated. NEC is no longer in the G3 category. Besides, MANEC was renamed as a mixed neuroendocrine-non-neuroendocrine tumor (MiNEN). In our study, we classified the G-NEN according to the latest WHO classification criteria. The results showed that NEC and MiNEN with a high degree of malignancy accounted for the majority, which may be related to the fact that most patients admitted to our hospital considered malignant tumors.

The multivariate analysis in our study implied that the T stage is an independent prognostic factor for G-NEN patients, which has been proved in another study[13]. Our data show that the mean survival time of patients with lymph node metastasis (28.62 months) is lower than that of patients without lymph node metastasis (54.53 months), but it is not statistically significant. But One study evaluating the prognostic significance of the number of involved loco-regional nodes indicated that patients with no positive nodes (N0), 1–6 positive nodes (N1) and those with more than six positive nodes (N2) showed distinct survival patterns {5-year OS N0: 70%(95%CI 65–75%), N1: 53%[95%CI 46–59] and N2: 18%[95%CI 9–29] p < 0.001} [14].

Four patients with gastric neuroendocrine neoplasms had distant metastasis at the time of diagnosis, while another 16 patients had distant metastases after surgery, and the most common was liver metastases. The higher rate of tumor metastasis may be related to the lack of standard chemotherapy, the later stage, and higher grade of tumor in the cohort. Univariate analysis showed that tumor infiltration depth was associated with tumor metastasis to some extent, while demographic characteristics, clinical characteristics, and other pathological characteristics (tumor location, tumor size, lymph node invasion, pathological grade, etc.) were not significantly associated with tumor metastasis.

Survival for all NEN has improved over time, especially for distant-stage NEN, reflecting improvement in therapies. However, the choice of treatment for G-NEN remains controversial. At present, surgery is the only cure method for locally advanced G-NEN, and it helps to increase the quality of life and overall survival in many patients with metastatic NEN[15]. The surgical procedure must consider personal risk factors of each patient, such as general health, additional illnesses, and tumor-specific factors, such as tumor stage, a grade of differentiation, functional activity, mass and variety of loco-regional as well as distant metastases, etc. In this study, all included 67 patients were treated with surgery. In the univariate analysis, we found that compared with open surgery, laparoscopic-assisted surgery is less invasive and significantly beneficial to the prognosis of patients( $p = 0.035$ ) (Table 3). Owing to some reasons that it is difficult to remove the tumor entirely with deep infiltration and the existence of distant metastasis, some patients received palliative resection. However, in our study, radical resection and palliative resection did not show a noticeable effect on the metastatic and survival time. But a related report from China emphasized the significance of surgical resection in improving disease-free survival and overall prognosis of patients with NEC or MiNEN in the stomach, even if distant metastasis was found when the G-NEN was diagnosis[16]. Galleberg's study[17] reported that GEP-NEN patients whose Ki-67 is less than 55% and underwent adjuvant chemotherapy can still benefit from liver metastasis resection or radiofrequency ablation. Some experts believed that locally advanced and metastatic disease should also be treated with extended resections[18].

Somatostatin analogs aiming to control tumor secretion or growth is the most attractive therapeutic option for patients with well-differentiated GEP-NEN[19]. For poorly differentiated G-NEN, radical surgery alone is not enough, so medical treatment should also be combined. Currently, available therapies include chemotherapy, targeted therapy, and peptide receptor radionuclide therapy (PRRT). Poorly-differentiated neuroendocrine carcinoma (NEC) is treated with cisplatin (or carboplatin) plus etoposide in first-line palliative chemotherapy[20]. In a study of systemic chemotherapy on GEP-NEC at 23 hospitals in Japan, irinotecan plus cisplatin (IP) and etoposide plus cisplatin (EP) were the most used regimens. G-NEN had a median total gastric survival of 13.3 months[21]. In our cohort, patients were usually treated in different hospitals after surgery. Of the patients who were followed, only 16 received adjuvant chemotherapy, and the regimens were quite different. Due to the small sample size, we only assessed the effect of chemotherapy or not on prognosis. More randomized controlled trials are needed to establish an appropriate chemical regimen for advanced NEN in the gastric digestive system. As for targeted therapy, everolimus demonstrated its high efficacy and tolerability, especially when in combination with other drugs in some clinical studies[22, 23]. PRRT has also been recognized as an alternative therapy for

unresectable or metastatic NEN, of which  $^{177}\text{Lu}$ -DOTATATE was approved to treat GEP-NEN patients in with SSTR positive expression among both Europe and the United States[24, 25]. Apart from them, supportive therapy cannot be ignored debulking surgery and interventional radiologic techniques to reduce tumors bulk or load, as well as systemic medical treatment options to manage or prevent hypersecretion syndromes and treatment-related side effects. What's more, supportive therapy also encompasses psychosocial support, expert nursing, nutritional support, and management of cancer-related pain[26, 27].

There are some limitations to our study. First, this is not a randomized controlled trial from a single-center study in China, So it's not ethnically representative. Second, Due to the low incidence of NEN in the population, the number of cases in our study was relatively small, and most patients belonged to NEC and MINEN. Third, because of our inadequate follow-up data and the uncertainty of the patient's chemotherapy regimen, we did not demonstrate a correlation between chemotherapy regimens and prognosis. But we confidently believe that the study could serve as useful background research for future clinical trials investigating G-NEN patients.

In conclusion, G-NEN is a kind of rare tumors that can occur at any part of the stomach. The clinical features are not specific. The tumor invasive depth related to tumor metastasis. The prognosis is associated with smoking, T stage, distant metastasis, and surgical method. Of them, the T stage is an independent prognostic factor for G-NEN patients. But more extensive studies are needed in the future.

## **Declarations**

### **Ethical approval**

This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of Shandong Provincial Hospital who determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted from the IRB of Shandong Provincial Hospital.

### **Consent for publication**

All the authors declare that they agree for the publication.

### **Availability of data and material**

Data supporting the conclusions of this article are included in the article

### **Competing Interest**

All the authors declare that they have no competing interests.

### **Funding**

This study was funded by the Key Technology Research and Development Program of Shandong (grant number 2019JZZY010104).

### Authors' contributions

Yajie Wang, Shubo Tian, and Leping Li designed the study. Yajie Wang, Kangdi Dong, Yuan Liu, and Hui Zhang collected the data. Yajie Wang, Wen Bei, and Hui Zhang followed up with the patients and analyzed the data. Yajie Wang wrote the manuscript. All authors approved the final version.

### Acknowledgments

Not applicable.

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## Figures

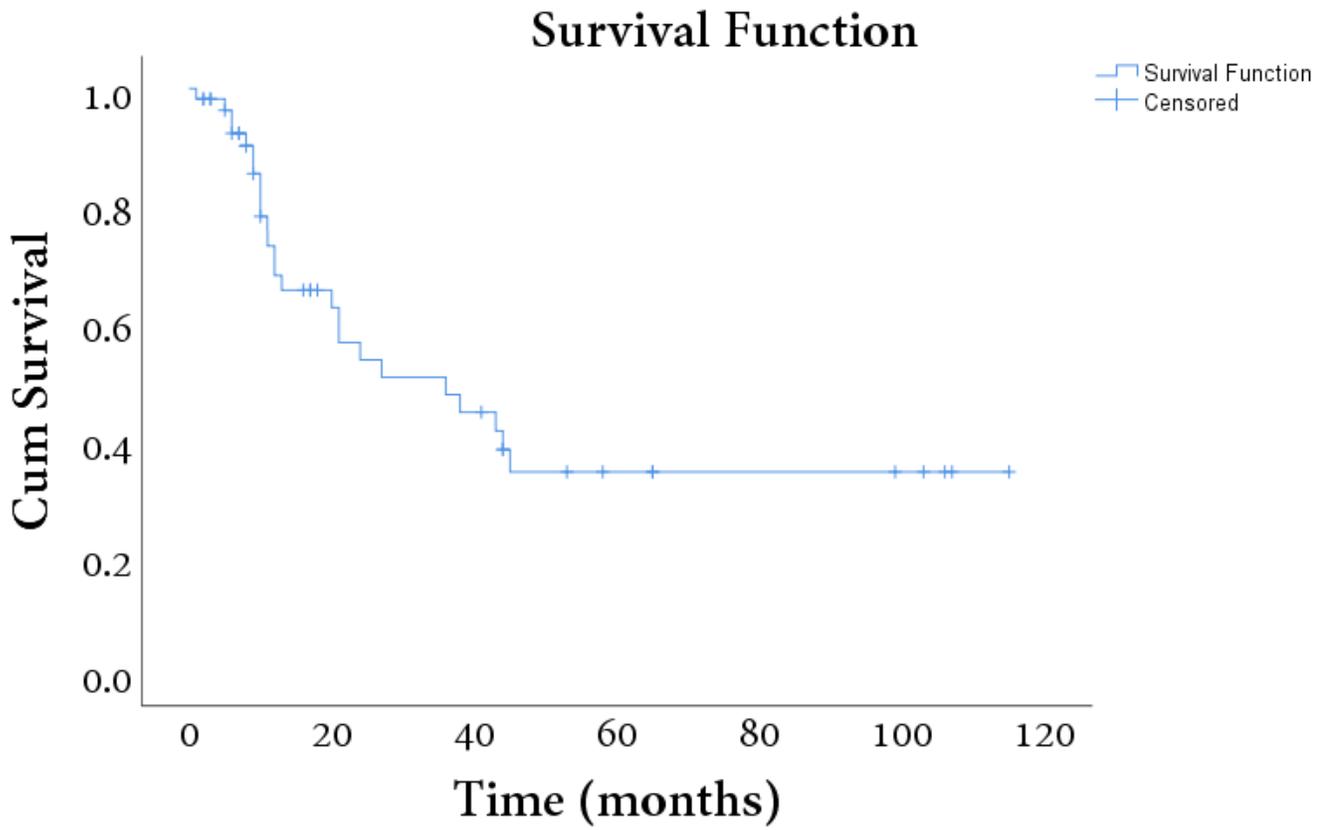
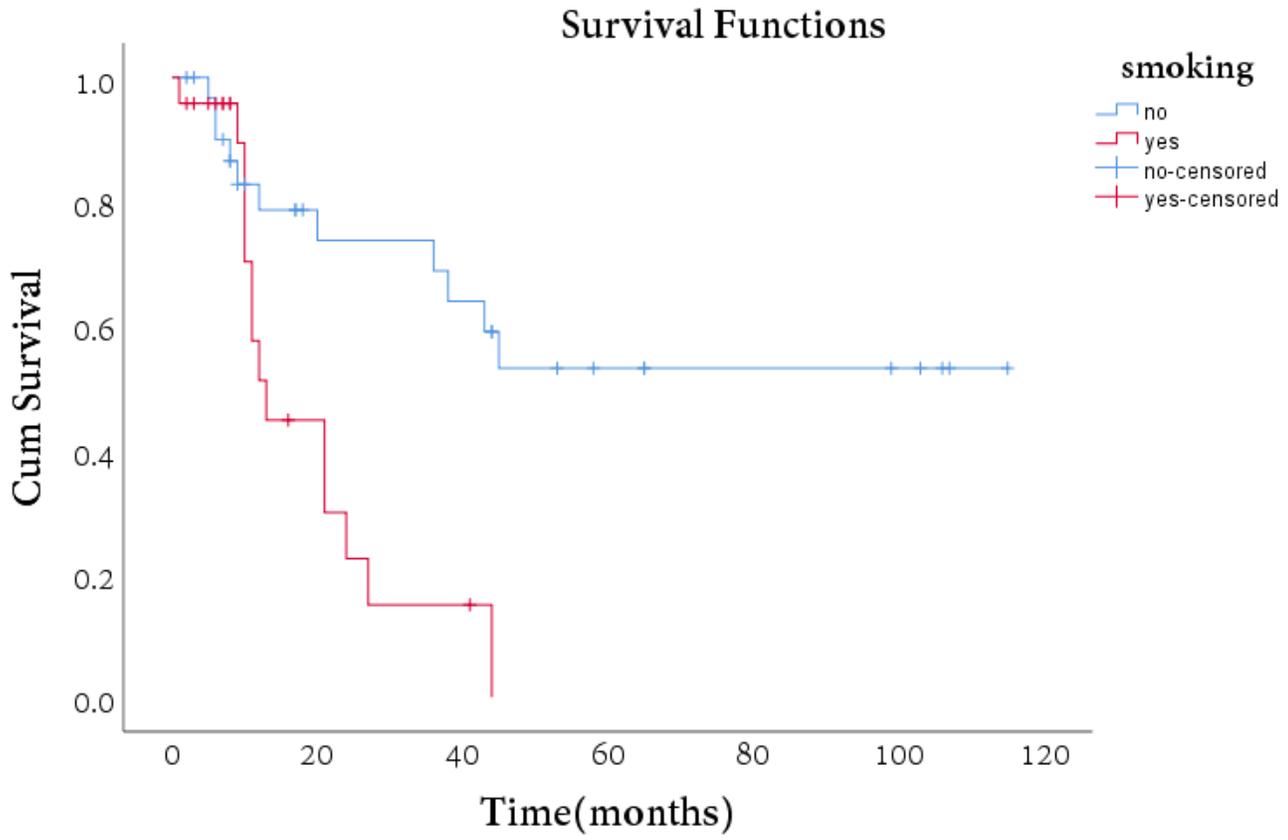


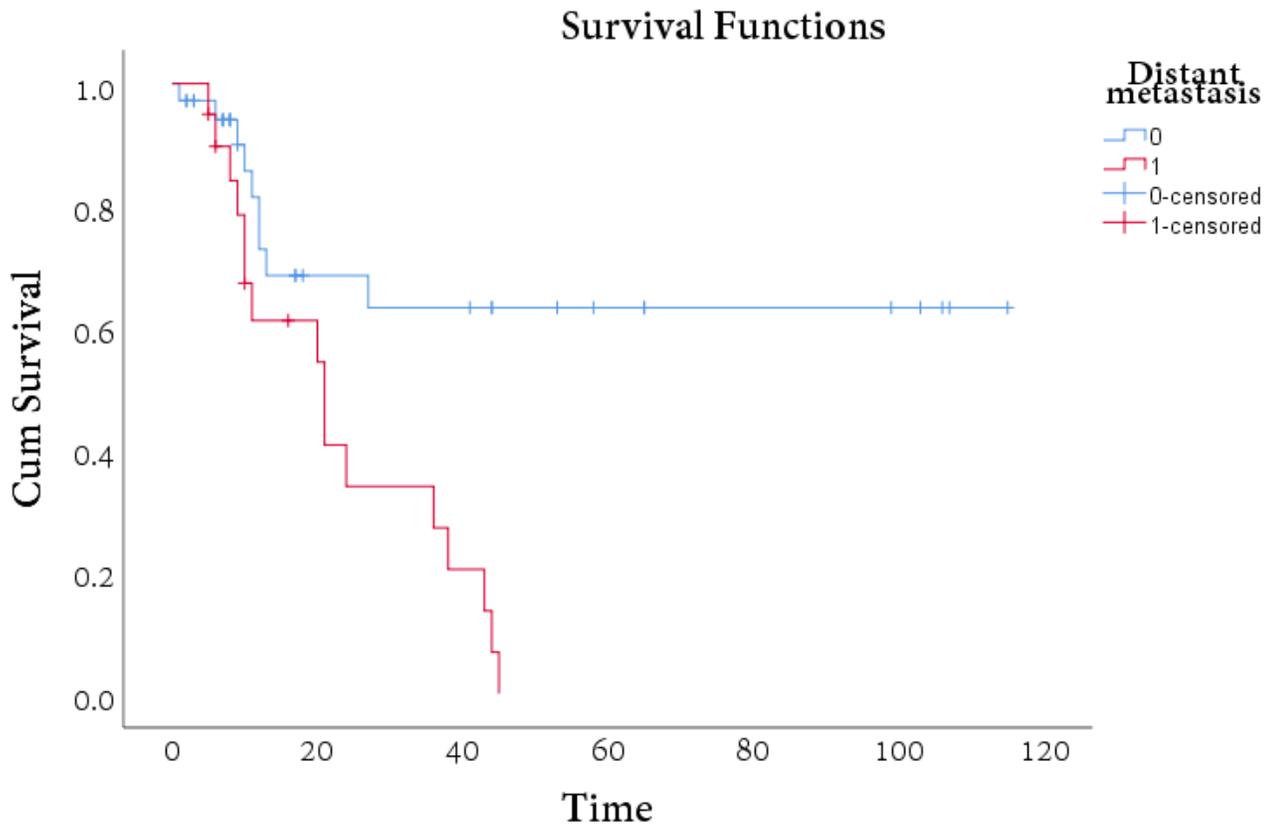
Figure 1

Kaplan-Meier analysis of overall survival. A. Overall survival in all included patients



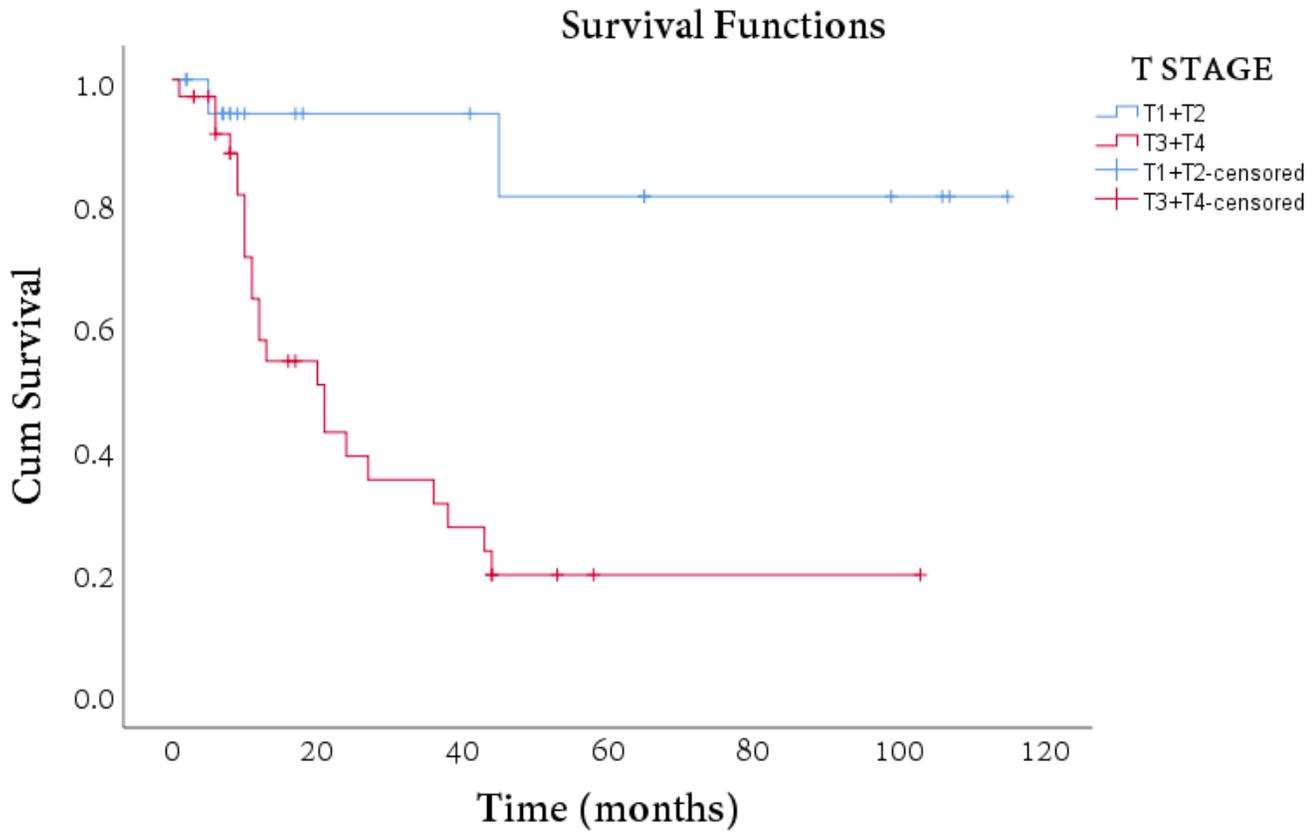
**Figure 2**

Kaplan-Meier analysis of overall survival. B. Overall survival by smoking or not



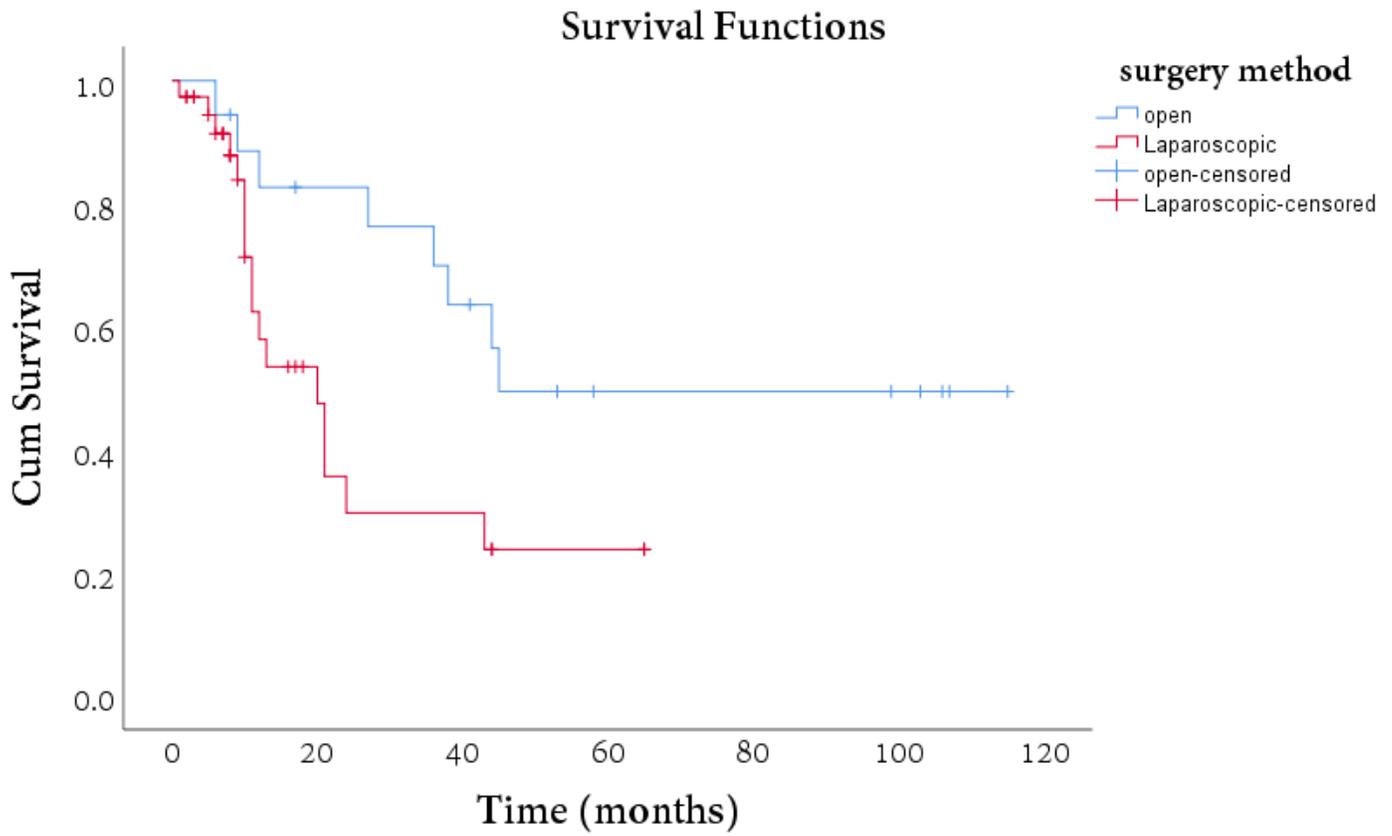
**Figure 3**

Kaplan-Meier analysis of overall survival. C. Overall survival by T staging.



**Figure 4**

Kaplan-Meier analysis of overall survival. D. Overall survival by distant



**Figure 5**

Kaplan-Meier analysis of overall survival. E. Overall survival by surgery method