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CEA Level, Radical Surgery, CD56 and CgA Expression Are Prognostic Factors for Patients With Locoregional Gastrin-Independent GNET

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Abstract: Gastrin-independent gastric neuroendocrine tumors (GNETs) are highly malignant. Radical resections and lymphadenectomy are considered to be the only possible curative treatment for these tumors. However, the prognosis of gastrin-independent GNETs is not well defined. In this study, we identified prognostic factors of locoregional gastrin-independent GNETs.

All patients diagnosed with locoregional gastrin-independent GNETs between 2000 and 2014 were included in this retrospective study. Clinical characteristics, blood tests, pathological characteristics, treatments, and follow-up data of the patients were collected and analyzed.

Of the 66 patients diagnosed with locoregional gastrin-independent GNETs, 57 (86.4%) received radical resections, 7 (10.6%) with palliative resection, 1 (1.5%) with gastrojejunostomy, and 1 (1.5%) with exploration surgeries. The median survival time for these patients was 19.0 months (interquartile range, 11.0–38.0). The 1-, 3-, and 5-year survival rates were 72%, 34%, and 28%, respectively. Multivariate analysis indicated that carcinoembryonic antigen (CEA) level ($P = 0.04$), radical resection ($P = 0.04$), and positive Cluster of Differentiation 56 (CD56) expression ($P = 0.016$) were significant prognostic factors on overall survival rate. Further univariate and multivariate analysis of 57 patients who received radical resections found that CgA expression ($P = 0.35$) and CEA level ($P = 0.33$) are independent prognostic factors.

Gastrin-independent GNETs had poor prognosis. Serum CEA level, radical surgery, CD56 and CgA expression are markers to evaluate the survival of patients with locoregional gastrin-independent GNETs.

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Abbreviations: AJCC = American Joint Committee on Cancer, CA19-9 = carbohydrate antigen 19-9, CD56 = Cluster of Differentiation 56, CEA = carcinoembryonic antigen, CgA = chromogranin A, CI = confidence interval, CT = computed tomography, DDP = cisplatin, ECL cell = enterochromaffin-like cell, ENETS = European Neuroendocrine Tumor Society, GEP-NET = gastroenteropancreatic neuroendocrine tumor, GNEN = gastric neuroendocrine neoplasm, GNET = gastric neuroendocrine tumor, HE = hematoxylin-eosin, HPF = high power field, HR = hazard ratio, IHC = immunohistochemistry, IQR = interquartile range, JGCA = Japanese Gastric Cancer Association, MEN1 = multiple endocrine neoplasm type 1, NSE = neuron-specific enolase, SEER = Surveillance Epidemiology and End Results, Syn = Synaptophysin, TNM = tumor, node, and metastasis, VP16 = Etoposide, WHO = World Health Organization, ZES = Zollinger–Ellison syndrome.

INTRODUCTION

Gastric neuroendocrine tumors (GNETs) are a rare type of tumor. These tumors arise from enterochromaffin-like cells that play a role in regulating gastric acid production. GNETs have increasingly been recognized because of the widespread use of upper gastrointestinal endoscopy.[1] According to Surveillance, Epidemiology, and End Results (SEER) database, the morbidity of GNETs has increased 10 times over the past 35 years.[2–4] GNETs comprise distinct tumor entities that differ in biological behavior and prognosis.[5]

GNETs are classified into gastrin-dependent and gastrin-independent types,[6] which range from benign to highly malignant biological behavior. Managing GNETs is affected by epidemiological, pathophysiological, endoscopic, and histological differences. Radical resections and lymphadenectomy are considered to be the only possible curative treatment of gastrin-independent GNETs.[7]

The prognosis of patients with gastrin-independent GNETs after surgery is not well defined because only a few studies have been conducted. The most commonly utilized scheme for the prognosis of these patients is the American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) staging

system[8] and European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines.[9] Although several tumor-specific morphological factors are associated with prognosis (e.g., tumor grading), other prognostic factors are not well defined mostly because of the small sample size in majority of the studies. In this work, we conducted a retrospective study to identify the prognostic factors of patients with locoregional gastrin-independent GNETs.

METHODS

Patients

With the approval of the Institutional Review Board, we retrospectively reviewed 74 consecutive surgical cases of gastrin-independent gastric neuroendocrine neoplasms (GNENs) registered between January 2000 and December 2014 at the Department of Abdominal Surgery in the Cancer Hospital of the Chinese Academy of Medical Sciences (China). Preoperative abdominal computed tomography (CT) scans were evaluated for indication for surgery. The general situation, presenting signs and symptoms, associated disease, tumor characteristics (number, size, site, and invasion), immunohistochemistry, and patient outcome, was analyzed, because lots of the patients' preoperative diagnoses were "gastric cancer," and octreotide scanning had not been widely used in China in previous years. Octreotide scanning was employed to exclude potential metastatic disease in 21 patients before surgery. After excluding 8 patients with distant metastases, 66 patients were finally examined. Clinical information was obtained from medical records.

Surgical Treatment and Pathological Examination

All the patients were surgically treated to achieve radical resections. Radical resections, which are referred to as gastric resection and D2 lymphadenectomy, were performed by experienced surgeons following the Japanese Gastric Cancer Association (JGCA) guidelines. Medicine oncologists designed the adjuvant treatment for all the patients. As there is no standard adjuvant therapy for gastrin-independent GNET patients, chemotherapy was advised if the patients had lymphatic metastasis or serosa invasion. Radiotherapy combined with chemotherapy was given to patients who had residual tumors after surgeries. The regimen of chemotherapy was EP (VP16 plus DDP) referring to the regimen of small cell lung cancer,[8] or other regimen including oxaliplatin, adriamycin, or paclitaxel.

Diagnosis of GNET was developed by pathologists according to the 2010 World Health Organization classification for neuroendocrine tumor. Pathological specimens were stained by hematoxylin-eosin. Diffuse and intense immunoreactivity of at least one of the well-known endocrine markers, namely, synaptophysin (Syn) and chromogranin A (CgA), confirmed the endocrine differentiation of tumor cells. Neural cell adhesion molecule Cluster of Differentiation 56 (CD56) was the auxiliary marker of CgA and Syn.

Follow-Up and Data Analysis

The follow-up program consisted of CT scans and endoscopic examinations every 6 months, blood tests, type-B ultrasonic, and chest radiograph every 3 months. Data were analyzed using SPSS 20.0 software. Overall survival was defined as the date of surgery to the date of death or the date of last follow-up for living patients. The Kaplan–Meier method was adopted to calculate cumulative survival, and the log rank test was used to analyze differences. The Cox proportional hazards regression model was used to identify independent prognostic factors. $P < 0.05$ was considered statistically significant.

RESULTS

Clinicopathological Outcomes

Gastrin-independent GNETs were common in aged (≥ 60 years) males. Comorbidity rate was 21.2% (n = 14). Approximately two-thirds of the cases were located in the fundus or cardia (n = 46). Overall, most of the patients exhibited symptoms attributable to mass effect, with dysphagia and abdominal pain being the most common presenting manifestations (n = 29 and 19).

Borrmann type II (ulcerative, with elevated distinct border) was the most common type and observed in 32 patients. CEA and CA19-9 (carbohydrate antigen 19-9) levels were elevated in 6 patients. Pernicious anemia was observed in 8 patients (Table 1).

Surgery and Pathological Outcome

Among all the participants, 57 (86.4%) patients received radical resections, 7 (10.6%) with palliative resection, 1 (1.5%) who had occlusion symptom with gastrojejunostomy, and 1 (1.5%) who had asymptomatic disease with exploration surgery. On purpose to reduce tumor burden and improve the effect of chemotherapy, palliative resections (including R1 or R2 operation) were performed when the tumors cannot be completely removed during operations, because of tumor invasion or encasement of major vessels.

The tumors appeared large (>5 cm) and single. Lymphatic metastases and serosa invasion were found in 57 and 24 patients, respectively. Seven and 59 patients were classified as stages II and III, according to the AJCC TNM Staging System for neuroendocrine tumors (stomach). Seven patients exhibited cancerous nodules. A total of 50 patients received adjuvant therapy, including chemotherapy and radiation therapy, after the operations. As there is no standard adjuvant therapy for gastrin-independent GNET patients, chemotherapy was advised if the patients had lymphatic metastasis or serosa invasion. Radiotherapy combined with chemotherapy was given to patients who had residual tumors after surgeries. The regimen of chemotherapy was EP (VP16 plus DDP) referring to the regimen of small cell lung cancer, or fluorouracil-based chemotherapy referring to the regimen of gastric cancer. The details of the pathological item, including mean tumor size, number of tumors, Ki-67 index, mitotic count in 10 High power field (HPF), and histological grade, are listed in Table 2.

Immunohistochemistry (IHC) found 66 patients to be Syn positive. CgA, neuron-specific enolase (NSE), and CD56 were detected positive in 53, 60, and 50 patients, respectively. The results of IHC detection of specific immunity indicators are summarized in Table 3.

Survival and Prognostic Factors

Follow-up was long-term in 62 of 66 patients. The median survival time of these patients was 19.0 months (IQR, 11.0–38.0). The 1-, 3-, and 5-year survival rates were 72%, 34%, and 28%, respectively.

An analysis was performed on the clinical, surgical, and pathological characteristics to identify the prognostic factors associated with survival. Univariate analysis confirmed that

TABLE 1. Summary of Clinical Characteristics and Overall Survival of Patients With Gastrin-Independent Gastric Neuroendocrine Tumors

	Number of Patients	Median, mo	IQR	χ^2	P^*
Gender				0.051	0.822
Male	56	20.0	10.0−26.0		
Female	10	16.0	11.0−38.0		
Age				0.456	0.5
<60	26	20.0	12.0−53.0		
≥60	40	19.0	10.0−29.0		
Comorbidity				1.246	0.264
Yes	14	18.0	11.0−40.0		
No	52	14.0	9.5−26.0		
Main symptoms				0.253	0.993
Abdominal pain	19	24.0	14.0−30.5		
Dysphagia	29	20.0	11.0−33.0		
Melena	7	12.0	10.0−19.5		
Body weight loss	6	19.0	9.0−21.0		
Other symptom	5	11.0	10.0−11.0		
Tumor location				0.257	0.879
Antrum	10	16.0	9.0−40.0		
Body	10	24.0	19.0−25.0		
Fundus or cardia	46	19.0	10.0−28.0		
Borrmann type[†]				2.967	0.397
I	9	11.0	9.0−19.0		
II	35	25.0	13.0−28.0		
III	21	20.0	9.0−28.0		
IV	1	10.0	NA		
CEA level				5.474	0.019
Normal	60	24.0	11.0−40.0		
Elevated	6	11.0	10.0−12.0		
CA19-9 level				1.809	0.179
Normal	60	20.0	11.0−28.0		
Elevated	6	11.0	10.0−14.0		
Pernicious anemia				0.063	0.801
Yes	8	19.0	10.0−29.0		
No	58	19.0	11.0−27.0		

CEA = carcinoembryonic antigen, CA19-9 = carbohydrate antigen 19-9, IQR = interquartile range.

*Log-rank test.

†Type I: polypoid fungating; type II: ulcerative, with elevated distinct border; type III: ulcerative with distinct border; type IV: diffused, indistinct border.

patients with radical resection, early TNM stage, and CgA positive exhibited higher survival rates than those with other types. However, elevated serum CEA level, lymphatic metastases or serosa invasion, and CD56 positive were poor predictors for survival (all $P < 0.05$). The statistical results for survival time and other data are provided in Tables 1–3. The survival curves are shown in Figure 1.

According to the Cox proportional hazards regression model, which removed the confounding factors, CEA level ($P = 0.04$), radical resection ($P = 0.04$), and CD56 positive ($P = 0.016$) had a significant effect on the overall survival rate (Table 4).

To avoid the possible confounding effects of radical resection, we excluded locoregional gastrin-independent GNETs cases treated with palliative resection (n = 7), gastrojejunostomy (n = 1), exploration (n = 1), and analyzed 57 patients with radical resection. Univariate analyses using a Cox regression model showed that CEA level ($P = 0.031$) and CgA expression ($P = 0.033$) were significantly associated

with overall survival (OS) (Table 5). However, TNM stage, lymphatic metastasis, serosa invasion, or CD56 expression were not associated with OS ($P > 0.05$). CEA level ($P = 0.033$) and CgA expression ($P = 0.035$) remained significant in multivariate analyses (Table 5).

DISCUSSION

Approximately 14% to 25% of GNETs are classified as gastrin-independent; these GNETs are large (>2 cm, mean 5.1 cm), usually occur singly, and grow from the gastric body/fundus in the context of normal (nonatrophic) surrounding mucosa.[10] GNETs can be divided into 3 types according to ENETS Consensus Guidelines.[9] Type I and II GNETs are gastrin-dependent, whereas Type III is gastrin-independent. Gastrin-dependent GNETs initiate because of hypergastrinemia causing hyperplasia of precursor enterochromaffin-like (ECL) cells. The hormone gastrin normally acts on ECL cells to regulate gastric acid production.[11] The hypergastrinemia of

TABLE 2. Summary of the Surgical, Pathological Characteristics, and Overall Survival of Patients With Gastrin-Independent Gastric Neuroendocrine Tumors

	Number of Patients	Median, mo	IQR*	χ^2	P*
Surgical resection				5.152	0.023
Radical	57	24.0	13.0–30.5		
Nonradical	9	11.0	9.0–13.0		
Lymphatic metastasis				4.312	0.038
Yes	57	16.0	10.0–53.0		
No	9	24.0	15.5–43.0		
Serosa invasion				4.225	0.039
Yes	24	13.0	9.0–27.0		
No	42	20.0	13.0–30.5		
Cancerous nodules				0.482	0.488
Yes	7	10.0	9.0–36.0		
No	59	19.0	12.0–24.5		
TNM stage†				3.937	0.047
II	7	31.0	22.0–43.0		
III	59	13.0	9.5–26.0		
Mean tumor size, cm				0.373	0.542
≤5	28	25.0	12.0–34.0		
>5	38	19.0	10.0–24.0		
Number of tumors				0.062	0.804
Single	63	19.0	14.0–28.0		
Multiple	3	14.0	NA		
Ki-67 index				0.036	0.805
≤50	25	24.0	9.5–28.0		
>50	41	19.0	10.0–25.0		
Mitotic count in 10 HPF				0.032	0.857
<20	36	38.0	15.0–42.0		
≥20	30	32.0	19.0–36.0		
Histological grade				NA	NA
G1	1	24.0	NA		
G2	1	11.0	NA		
G3	64	15.5	10.0–29.0		
Adjuvant therapy				2.186	0.138
Yes	50	25.0	9.5–30.5		
No	16	26.0	10.0–48.0		

HPF = high power field, IQR = interquartile range, NA = not applicable.
*Log-rank test.
†Tumor stage was defined according to the AJCC TNM staging system.

gastrin-dependent GNETs are caused by the conditions associated with achlorhydria, such as chronic atrophic gastritis, vagotomy, and chronic acid suppression treatment, or autonomous gastrin secretion from a gastrinoma (Zollinger–Ellison syndrome) or multiple endocrine neoplasm type 1.[12–14] However, gastrin-independent GNETs occur sporadically without evidence of a predisposing condition, like atrophic gastritis or a gastrinoma, that lead to hypergastrinemia. There is an absence of ECL hyperplasia in the corpus mucosa that is evident in gastrin-dependent GNETs.[15]

In contrast to gastrin-dependent GNETs, gastrin-independent GNETs may be aggressive and mimic the course of gastric adenocarcinoma. These GNETs require radical oncological therapies. The overall 5-year survival of gastrin-independent GNETs ranges from 22% to 30%,[16] which was similar to our data.

GNETs are more common in male patients. The average age of onset is 55 years. Our study showed that the male/female ratio was 5.6:1. The incidence of proximal gastric fundus and cardia region accounted for 69.7%, which is similar to those in literature.[7] The clinical symptoms of gastrin-independent GNETs lack specificity, which resemble a typical carcinoid syndrome. In this group, the main syndrome of patients was abdominal pain and dysphagia. No patient exhibited carcinoid syndrome symptoms.

Resection is the primary treatment approach for most localized carcinoid tumors. Although current options for gastrin-dependent GNETs include simple surveillance, endoscopic polypectomy, surgical excision with or without surgical antrectomy, or total gastrectomy,[17] a universal consensus on the use of surgical treatment of gastrin-independent GNET exists. Complete surgical resection is associated with better long-term survival.[18] Radical resections, which are referred to as gastric resection and D2 lymphadenectomy, were performed by experienced surgeons following the JGCA guidelines. Gastrin-independent GNETs represent highly malignant tumors with strong

TABLE 3. Summary of the IHC Detection of Specific Immunity Indicator Characteristics and Overall Survival of Patients With Gastrin-Independent Gastric Neuroendocrine Tumors

Specific Immunity Indicators	Number of Patients	Median, mo	IQR	χ^2	P^*
CgA				4.052	0.044
Positive	53	24.0	11.0–34.0		
Negative	13	12.0	9.0–19.0		
NSE				0.039	0.844
Positive	60	13.0	9.0–36.0		
Negative	6	15.0	12.0–20.0		
Syn				NA	NA
Positive	66	14.0	9.5–27.0		
Negative	0	NA	NA		
CD56				6.32	0.012
Positive	54	12.5	9.0–19.0		
Negative	12	39.0	14.0–63.0		

CD56 = Cluster of Differentiation 56, CgA = Chromogranin A, IHC = immunohistochemistry, IQR = interquartile range, NSE = neuron-specific enolase, Syn = Synaptophysin.

*Log-rank test.

invasive and metastatic potential although the locoregional diseases are usually presented with extensive local lymph node metastasis and invasion to adjacent organs. The goal of radical resections is impossible to achieve in every localized gastrin-independent GNET patients. Our study showed that 57 of 66 patients received radical surgeries and achieved better survival than those with palliative surgeries (Figure 1). Surgical resection is only advised for G1 and G2 patients with liver metastases.[19,20] However, Du et al[21] reported that grade 3 gastroenteropancreatic neuroendocrine tumor patients with liver metastases also benefit from surgery. For locoregional unresectable and/or metastatic carcinoid tumors, cytoreductive surgery or ablative therapies such as radiofrequency ablation or cryoablation may be considered if near-complete treatment of tumor burden can be achieved because of the poor efficacy of chemotherapy and radiotherapy.[22–25] But it remains controversial.

In recent years, increasing attention has been given to the relation between CD56 and tumor progression. CD56 expression is an independent adverse risk factor for patients with acute myeloid leukemia with t (8;21)[26] and patients with acute promyelocytic leukemia with high initial white blood cell counts.[27–29] Simultaneous expression of CD56 and CgA ($P < 0.04$) is significantly associated with poor outcomes in large-cell neuroendocrine carcinoma, which is a rare neuroendocrine pulmonary malignancy.[30] Neural cell adhesion molecule, also called CD56, is a group of cell surface glycoproteins that are involved in direct cell–cell adhesion and induce biological effect. It is involved in the adhesion, detachment, and aggregation of malignant cells.[31] CD56 of neuroendocrine neoplasms is highly expressed on immunophenotyping.[32–34] Sufficient and deep layer of IHC detection helps improve the diagnostic accuracy for NETs. Syn, CgA, and CD56 are neuroendocrine differentiation markers that are important for diagnosing neuroendocrine carcinoma, particularly CgA, which is secreted by the neuroendocrine cells. However, scarcely any research has determined the association of IHC markers with prognosis in GNET patients. Our study found that CD56 and CgA expression were associated with survival of GNETs. Multivariate analysis indicated that CD56 is an independent prognostic factor. CD56 may be a reliable targeted protein for therapy. Geertsen et al[35] reported that IFN-gamma exhibits a weak upregulating effect in CD56 expression.

IMGN901 (lorvotuzumab mertansine), a new antibody-drug conjugate, was developed to target and kill CD56-positive cancer cells.[36] As it had been found that, the immunogenicity of CgA in NET tissue decreased or even disappeared with the decreasing of tumor's differentiation. Maybe the morphology and function of well-differentiated NET cells are similar with normal neuroendocrine cells, but secretory granules in poorly differentiated NET cells are rare,[37] indicating that expression of CgA correlated with the differentiation of NET and CgA may be a prognostic marker of gastroenteropancreatic neuroendocrine tumor (GEP-NET). There have been several studies reporting that serum CgA levels are associated with survival of GEP-NET patients.[38,39] But few studies reported the relationship of CgA expression on immunohistochemical staining and prognosis in NET patients. Wang et al[40] analyzed the patients with gastrointestinal NETs and found that the survival rate after 1 and 2 years for patients with CgA expression was significantly higher than that for patients without CgA expression. Their finding corroborates our further result of the multivariate analysis of 57 patients with locoregional gastrin-independent GNET who received radical resections. After precluding 9 patients who received nonradical resection, we found that CgA expression and CEA level are independent prognostic factors.

The association between GNETs and tumor markers has not been well investigated because of its rarity. The concept of serum tumor marker represents a quantifiable assessment of the tumor burden at that time. Using tumor markers involve several aspects, such as determination of cancer risk, screening, diagnosis, prognosis, prediction of response to therapy, and monitoring disease course.[41–43] Blood CgA is the best tumor marker for neuroendocrine carcinoma. The specificities of biomarkers in GEP-NET patients were 86% for CgA, 100% for NSE, 91% for CEA, and 100% for 5-hydroxyindoleacetic acid (5-HIAA). The corresponding sensitivities were 68% for CgA, 33% for NSE, 15.4% for CEA, and 35% for 5-HIAA.[44] Serum CgA test was only performed in very few hospitals in China. Thus, in our center, CEA and CA19-9 were routinely tested for each patient with GNET, although these markers are not as sensitive as CgA for GNETs. CEA is a carbohydrate antigen extracted from the tissues of patients with digestive tract cancer, and it is a related antigen of digestive tract neuroendocrine carcinoma. When a
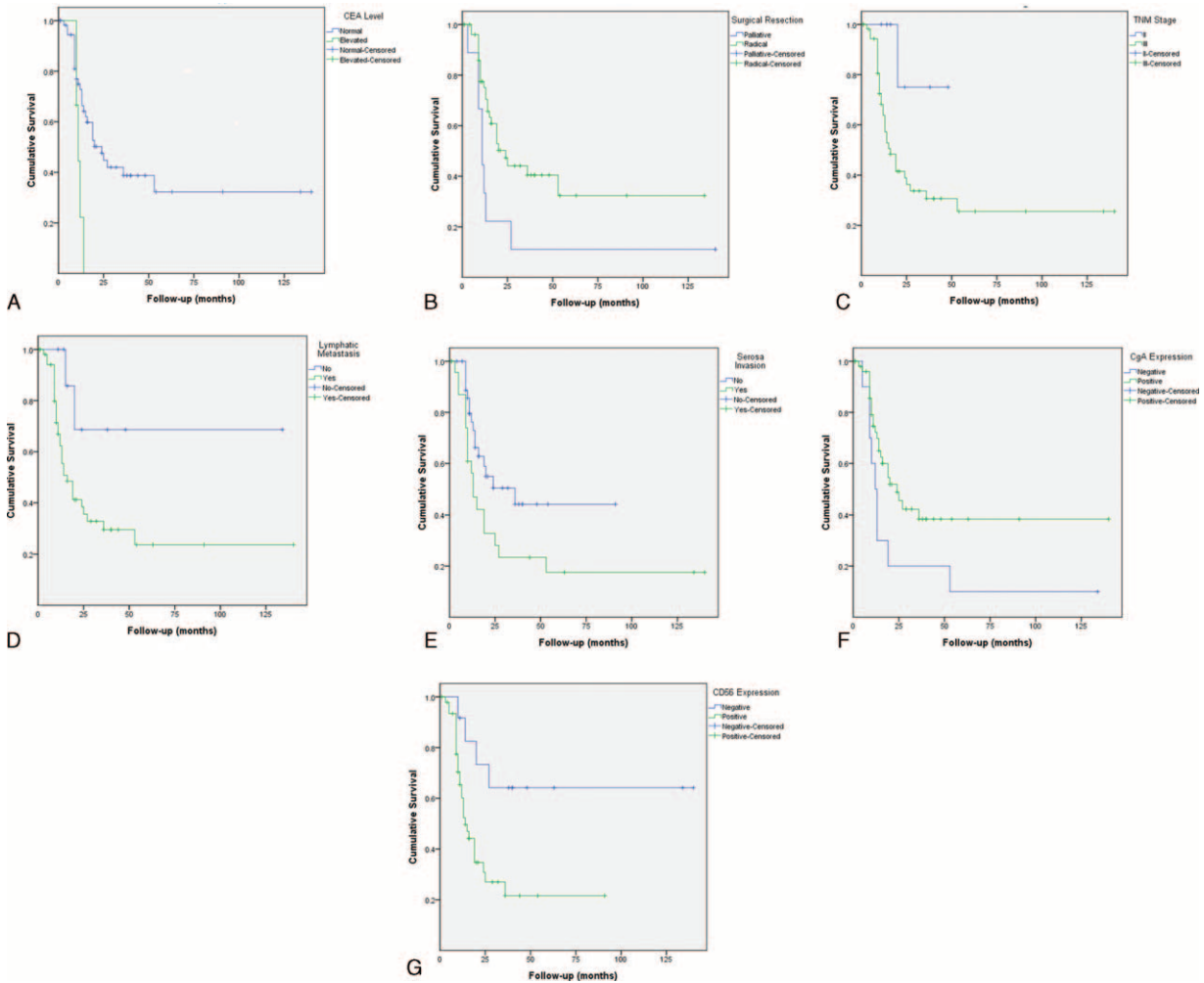
FIGURE 1. Comparison of survival time among CEA level (A), surgical resection (B), TNM stage (C), lymphatic metastasis (D), serosa invasion (E), CgA expression (F), and CD56 expression (G). CD56 = Cluster of Differentiation 56, CEA = carcinoembryonic antigen, CgA = chromogranin A, TNM = tumor, node, and metastasis.

cell is cancerous, the protease and activity of the enzyme in the cell membrane increase and the cell cytoskeleton is destroyed, causing the cell surface antigen to litter. Thus, the serum CEA content increases. We are interested to determine whether CEA level is an independent prognostic factor of GNETs through multivariate analysis. We suggest that serum CEA should be tested in every GNET patient. In summary, serum CEA can be utilized to monitor the treatment for patients with gastrointestinal neuroendocrine carcinoma, tumor recurrence, and metastasis.

Clinical doctors commonly use tumor invasion, lymphatic metastases, and TNM stage to anticipate survival because the biological behavior of gastrin-independent GNETs is sometimes similar to gastric adenocarcinoma. However, we should also focus on the unique factors in GNETs, such as Ki-67 index and IHC markers. Aside from these prognostic factors, Ki-67 index is a widely accepted factor in predicting survival in NETs.[23] Ki-67 index was not an independent prognostic factor in our study because almost all the Ki-67 index of our patients were high.

TABLE 4. Multivariate analysis of serum CEA level, radical surgery, TNM stage, lymphatic metastasis, serosa invasion, CgA expression, and CD56 expression for the influence on survival

	B	**SE**	**Wald**	**P^***	**OR**
CEA level	−1.109	0.539	4.237	0.040	0.330
Surgical resection	0.959	0.467	4.214	0.040	2.609
TNM stage	0.028	1.483	0.000	0.985	1.028
Lymphatic metastasis	−0.457	1.096	0.174	0.677	0.633
Serosa invasion	−0.563	0.389	2.099	0.147	0.569
CgA expression positive	0.831	0.439	3.591	0.058	2.296
CD56 expression positive	−1.481	0.613	5.834	0.016	0.227

CEA = carcinoembryonic antigen, CgA = chromogranin A, CD56 = Cluster of Differentiation 56, OR = odds ratio, SE = standard error, TNM = tumor, node, and metastasis.
*Cox regression analysis.

TABLE 5. Overall survival of 57 patients with radical resections

Prognostic Factor	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
CEA level				
Normal (n = 52)	1		1	
Elevated (n = 5)	3.572 (1.124–11.354)	0.031	3.543 (1.106–11.351)	0.033
TNM stage				
II (n = 7)	1		—	
III (n = 50)	4.914 (0.664–36.352)	0.119	—	—
Lymphatic metastasis				
No (n = 9)	1		—	
Yes (n = 48)	3.418 (0.807–14.481)	0.095	—	—
Serosa invasion				
No (n = 40)	1		—	
Yes (n = 17)	1.930 (0.888–4.199)	0.097	—	—
CgA				
Negative (n = 10)	1		1	
Positive (n-47)	0.399 (0.171–0.928)	0.033	0.402 (0.173–0.937)	0.035
CD56				
Negative (n = 12)	1		—	
Positive (n = 45)	3.082 (0.912–10.148)	0.070	—	—

CD56 = Cluster of Differentiation 56, CEA = carcinoembryonic antigen, CI = confidence interval, HR = hazard ratio, TNM = tumor, node, and metastasis.

CONCLUSIONS

Gastrin-independent GNETs are rare tumors that must be treated with radical surgery if no distant metastases are present. Our study indicated that radical surgery, serum CEA level, IHC marker CD56 and CgA are important for the prognostic evaluation of locoregional gastrin-independent GNET patients. To the best of our knowledge, this study is the first to report that serum CEA level and IHC marker-CD56 are independent prognostic factors for GNET patients. Our study is limited by the low morbidity of this disease; obtaining a large sample size in a center is impossible. Further multicenter research should be carried out to achieve more accurate results.

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