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ORIGINAL ARTICLE

Retrospective Study

Clinicopathological, treatment, and prognosis study of 43 gastric neuroendocrine carcinomas

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Abstract

AIM

To provide more information and therapeutic methods about gastric neuroendocrine carcinomas (G-NECs) which occur rarely but are highly malignant and clinically challenging.

METHODS

We retrospectively analyzed the clinicopathological characteristics, treatments, and prognosis of 43 G-NEC patients at our hospital between January 2007 and December 2014. The diagnosis was based on the 2010 World Health Organization criteria.

RESULTS

Forty-three G-NECs containing 39 small cell carcinomas and 4 large cell NECs with Ki67 > 60% were included in this study, accounting for only 0.95% of all gastric carcinomas. The median patient age was 62 years

(range, 33-82) and the male-to-female ratio was 4.4:1. All patients underwent surgery, including 38 curative resections and 5 palliative resections. Among these 43 patients, nearly half (48.84%) of these tumors were located in the cardiac region of the stomach, regional lymph node metastasis was found in 31 cases (72.09%), and liver metastasis was found in 6 cases (13.95%). Follow-up information was got for 40 patients. Twenty-three die of this disease with a median survival of 31 mo (range 1-90). The 1-year, 2-year, 3-year, and 5-year survival rate was 77.50%, 57.04%, 44.51%, and 35.05%, respectively. Survival was better in patients with tumor located in the cardiac region of the stomach, less than 7 lymph nodes metastasis and no liver metastasis. Five patients did not undergo postoperative chemotherapy, and the median survival time for these patients was 15 mo. For the remaining 34 patients who received postoperative chemotherapy, the median survival time was 44 mo and those received etoposide, cisplatin, and Paclitaxel survived the best. One patient with resected liver metastasis who received postoperative Capecitabine plus Oxaliplatin and Paclitaxel systemic chemotherapy plus octreotide LAR (30 mg intramuscularly, every 4 wk, for 2 years) has survived for 74 mo with no recurrence.

CONCLUSION
G-NECs are mostly nonfunctioning, which lead to a delay in detection. Local and/or distant metastases were noticed in most patients when diagnosed, and they required postoperative medical treatment. Adjuvant etoposide, cisplatin plus Paclitaxel systemic chemotherapy is recommended for these patients.

Key words: Gastric neuroendocrine carcinomas; Liver metastasis; Medical treatment; Surgery; Prognosis

Core tip: This is a retrospective study to provide more information and therapeutic methods about gastric neuroendocrine carcinomas. In this study we found that local and/or distant metastases were noticed in most patients when diagnosed, and they required postoperative medical treatment. Adjuvant etoposide, cisplatin plus Paclitaxel systemic chemotherapy is recommended for these patients.

INTRODUCTION

Neuroendocrine neoplasms (NENs), which used to be called neuroendocrine tumors (NETs), are a group of pathologically and clinically heterogeneous tumors with benign to high-grade malignant behavior. These tumors are considered uncommon, but can occur in almost every site throughout the body, especially in the lung, small intestine, rectum, pancreas, stomach, cecum, colon, appendix, and thymus[1]. And more than half of extra-pulmonary NENs occur in digestive tract.

It is now believed that NENs originate from the diffuse neuroendocrine cell system. In the gut and pancreas, these cells locate in the mucosa of the gastrointestinal tract or form islets in the pancreas, deriving from multipotent stem cells[2,3]. While most gastroenteropancreatic NENs (GEP-NENs) are clinically silent, some can secrete hormones and amines, causing carcinoid syndrome and other clinical syndromes. For nonfunctioning NENs, early detection might be difficult, which can delay diagnosis by several years, unless the primary or metastatic lesions have grown large enough to cause symptom[3].

In the past several decades, the incidence of NENs has increased over time[4,5], from 1.09/100000 in 1973 to 5.25/100000 in 2004 in the United States[1]. However, there seemed to be no improvement in outcomes, because of our limited understanding of this disease and a lack of uniform pathology classification and staging system[6,7]. More recently, increasing attention has been paid to this condition, and in 2010, the World Health Organization (WHO) issued a new classification. According to this classification, GEP-NENs can be categorized as NET G1 or NET G2, or neuroendocrine carcinoma (NEC) G3. NET G1 or G2 are composed of tumor cells with well differentiated morphology and Ki67 $\leqslant$ 20%, while NECs have poorly differentiated histology with Ki67 > 20%[8]. And NECs are characterized by high-grade cytological atypia, apparent pleomorphism, extensive necrosis, and prominent mitotic activity[9].

Gastric neuroendocrine carcinomas (G-NECs) are a group of poorly differentiated tumors with high-grade malignancy, and can be either small-cell carcinomas or large-cell NECs. Epidemiological, clinical and treatment data is lack for these patients and little is got for prognostic and predictive factors. Therefore, we report the medical records of 43 patients with G-NECs that met the definition of the updated (2010) WHO classification. And to our knowledge, this report is one of sizable series of G-NECs so far.

MATERIALS AND METHODS

This was a retrospective study. All G-NECs treated in Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University from 2007 to 2014 were investigated. All of them were local people of South China. The diagnosis, grading, and staging were performed according to the 2010 WHO classification[8]. TNM staging was evaluated in accordance with the 7th Edition of the AJCC Cancer's TNM Classifcation[10]. Information on age, gender, tumor

Table 1 Clinical characteristics of 43 gastric neuroendocrine carcinomas	
Clinicopathological features	***n* (%)**
Age (yr)	
< 60/⩾ 60	15 (34.88)/28 (65.12)
Mean ± SD	62.26 ± 10.46
Gender	
Male/Female	35 (81.40)/8 (18.60)
Tumor location	
Cardiac	21 (48.84)
Corpus	10 (23.26)
Antrum	10 (23.26)
Residual stomach anastomosis	2 (4.65)
Tumor size (max diameter, cm)	
⩽ 5/> 5	20 (46.51)/23 (53.49)
Mean ± SD	5.47 ± 3.18
T classification	
T1	0 (0)
T2	4 (9.30)
T3	0 (0)
T4	39 (90.70)
Lymph node metastasis	
N0/N1	12 (27.91)/31 (72.09)
Liver metastasis	
Absent/present	37 (86.05)/6 (13.95)
Pathological stage	
I / II / III / IV	0 (0)/2 (4.65)/35 (81.40)/6 (13.95)
Pathology	
Small cell carcinomas	39 (90.70)
Large cell carcinomas	4 (9.30)
Operation	
Curative resection	38 (88.37)
Palliative resection	5 (11.63)
Neoadjuvant therapy	
No/present	100 (100)/0 (0)
Adjuvant chemotherapy	
No-chemotherapy/present/lost	5 (11.63)/34 (79.07)/4 (9.30)
Follow-up	
Median OS (mo)	31.0
Dead/alive/lost	23 (53.49)/17 (39.53)/3 (6.98)

Patients were staged in accordance with the 7th Edition of the AJCC Cancer's TNM Classification. OS: Overall survival.

size, tumor location, T classification, lymph node metastasis, liver metastasis, pathological stage, pathology, treatment and outcome were reviewed. The overall survival (OS) time was calculated from the date of surgery to death, or August 30, 2016, the ultimate follow-up deadline. The research was approved by the Research Ethics Committee of Ren Ji Hospital and all participants were provided with written informed consent before enrolment in this study. Cases with mixed tumors were excluded.

Statistical analysis was performed using SPSS version 22.0 software (IBM Corp., Armonk, NY, United States). Graphical representations were carried out with Graph Pad Prism 6 (San Diego, CA, United States). Data were presented as the means ± SD. The survival calculations were illustrated with Kaplan-Meier curves and differences between survival curves were tested by the log-rank test. Cox proportional hazards model was used to identify the prognostic factors by univariable analysis. *P* values (two-sided) less than 0.05 were

considered statistically significant.

RESULTS

Forty-three patients were enrolled in this study, accounting for 0.95% of all patients with gastric carcinoma. They were 35 males and 8 females, ranging in age from 33 to 82 years, with a median of 62 years (Table 1).

The most common initial clinical symptoms were intermittent upper abdominal pain or discomfort (*n* = 29, 67.44%), followed by obstruction (*n* = 8, 18.60%) and gastrointestinal bleeding (*n* = 4, 9.30%). Two cases were found accidentally during endoscopy, and none of these patients suffered characteristic hormonal syndromes.

All patients underwent surgery, including 38 curative resections and 5 palliative resections because of liver metastases (Table 1). Of the 6 liver metastases, 1 had resection of both primary and metastatic tumors, and the other 5 received palliative primary tumor resection only. We found that nearly half (*n* = 21, 48.84%) of these tumors were located in the cardiac region of the stomach, and the others occurred in the gastric corpus (*n* = 10, 23.26%), gastric antrum (*n* = 10, 23.26%), and residual stomach anastomosis (*n* = 2, 4.65%). The maximum diameters of these tumors ranged from 0.8 to 22.0 cm, with a mean maximum diameter of 5.47 cm. Among these 43 patients, regional lymph node metastasis was found in 31 cases (72.09%), and liver metastasis was found in 6 cases (13.95%). TNM stages were as follows: stage II in 2 patients, stage III in 35 patients, and stage IV in 6 patients (Table 1)

The Ki67 indices were 60%-85%, determined by the immunohistochemistry. And in pathology, there were 39 small cell carcinomas and 4 large cell NECs.

Patients were followed up for 1 to 90 mo, and information was available for 40 patients. By the ultimate follow-up deadline, 23 patients have died of this disease. The total median survival was 31.0 mo (range 1-90) and the 1-year, 2-year, 3-year, and 5-year survival rate was 77.50%, 57.04%, 44.51%, and 35.05%, respectively (Figure 1). By evaluating potential survival factors, such as age, gender, tumor location, tumor size, T classification, lymph node metastasis number and liver metastasis utilizing univariable Cox regression analysis and Kaplan-Meier analysis, we found that tumor location, lymph nodes metastasis and live metastasis were associated with OS of G-NEC patients, and survival after surgery was better in patients with tumor located in the cardiac region of the stomach (median survival: 48.0 (Car) *vs* 16.25 (Cor)/19.0 (Ant)/45.5 (Rsa) months, Car *vs* Ant, *P* = 0.0742; Car *vs* Cor, *P* = 0.0152), less than 7 lymph nodes metastasis (median survival: 44.0 mo *vs* 15.0 mo, *P* = 0.0233) and no liver metastasis (median survival 38.0 mo *vs* 8.25 mo, *P* = 0.0096) (Table 2

Table 2 Univariable analysis of prognostic parameters for survival in Ren Ji cohort patients with gastric neuroendocrine carcinomas

Prognostic parameter	Univariable analysis		
	HR	95%CI	*P* value
Age (yr)			
< 60	1.0 (reference)		
⩾ 60	2.718	0.921-8.023	0.070
Gender			
Male	1.0 (reference)		
Female	0.915	0.308-2.718	0.873
Tumor location			
Cardiac	1.0 (reference)		
Corpus	3.034	1.100-8.374	0.032
Antrum	2.331	0.817-6.648	0.114
Residual stomach anastomosis	1.401	0.176-11.159	0.750
Tumor size			
⩽ 5 cm	1.0 (reference)		
> 5 cm	1.605	0.693-3.717	0.269
T classification			
T1 + T2	1.0 (reference)		
T3 + T4	0.760	0.407-1.420	0.390
Lymph node metastasis			
⩽ 7	1.0 (reference)		
> 7	2.766	1.101-6.948	0.030
Liver metastasis			
Absent	1.0 (reference)		
Present	3.515	1.269-9.731	0.016
Adjuvant chemotherapy			
No-chemotherapy	1.0 (reference)		
Present	0.226	0.076-0.674	0.008
Chemotherapy regimen			
No-chemotherapy	1.0 (reference)		
EP	0.138	0.029-0.667	0.014
EP + PTX	0.059	0.012-0.298	0.001
Other chemotherapy	0.426	0.140-1.296	0.133

The bold number represents the *P* values with significant differences. EP: Etoposide plus cisplatin; EP + PTX: EP plus Paclitaxel.
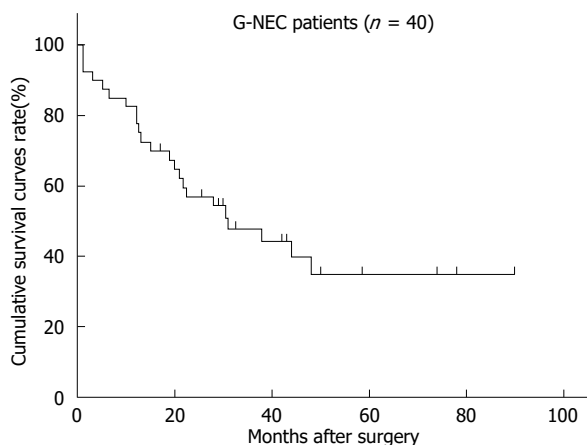
Figure 1 Survival curves of the 40 cases of gastric neuroendocrine carcinomas. G-NECs: Gastric neuroendocrine carcinomas.

and Figure 2A-C). There was no difference in survival between the small cell carcinoma and large cell neuroendocrine carcinoma (data and figure not shown).

After surgery, among the 43 patients, 5 patients did not undergo chemotherapy, 4 patients failed in follow-up of chemotherapy regimens, 6 patients received adjuvant etoposide plus cisplatin (EP) systemic chemotherapy, 11 patients received adjuvant EP plus Paclitaxel (EP + PTX) systemic chemotherapy, 3 patients (2 stage Ⅲ, 1 stage Ⅳ) received adjuvant Gimeracil and Oteracil Potassium capsule only chemotherapy. The remaining 14 patients received Fluoropyrimidine-based regimens, such as 5-fluorouracil/leucovorin/oxaliplatin combination regimen (FOLFOX) and Capecitabine plus Oxaliplatin. By analyzing the effect of these different regimens, we found that the 3-drug regimen (EP + PTX) [median survival: undefined (8 alive and 3 dead)] and EP regimen (median survival: 48.25 mo) produced a dramatically longer OS than no-chemotherapy (median survival: 15 mo, EP + PTX *vs* no-chemo, $P < 0.0001$; EP *vs* no-chemo, $P = 0.0085$), and EP + PTX regimen exhibited a better improvement than EP regimen, but it didn't reach a statistical significance ($P = 0.3188$; Table 2 and Figure 2D).

It is worth mentioned that, in this study, 1 patient with resected liver metastasis and postoperative Capecitabine plus Oxaliplatin and Paclitaxel systemic chemotherapy plus octreotide LAR (30 mg intramuscularly, every 4 wk, for 2 years) has survived for 74 mo with no recurrence.

DISCUSSION

In 1907, Oberndorfer first differentiated NENs from
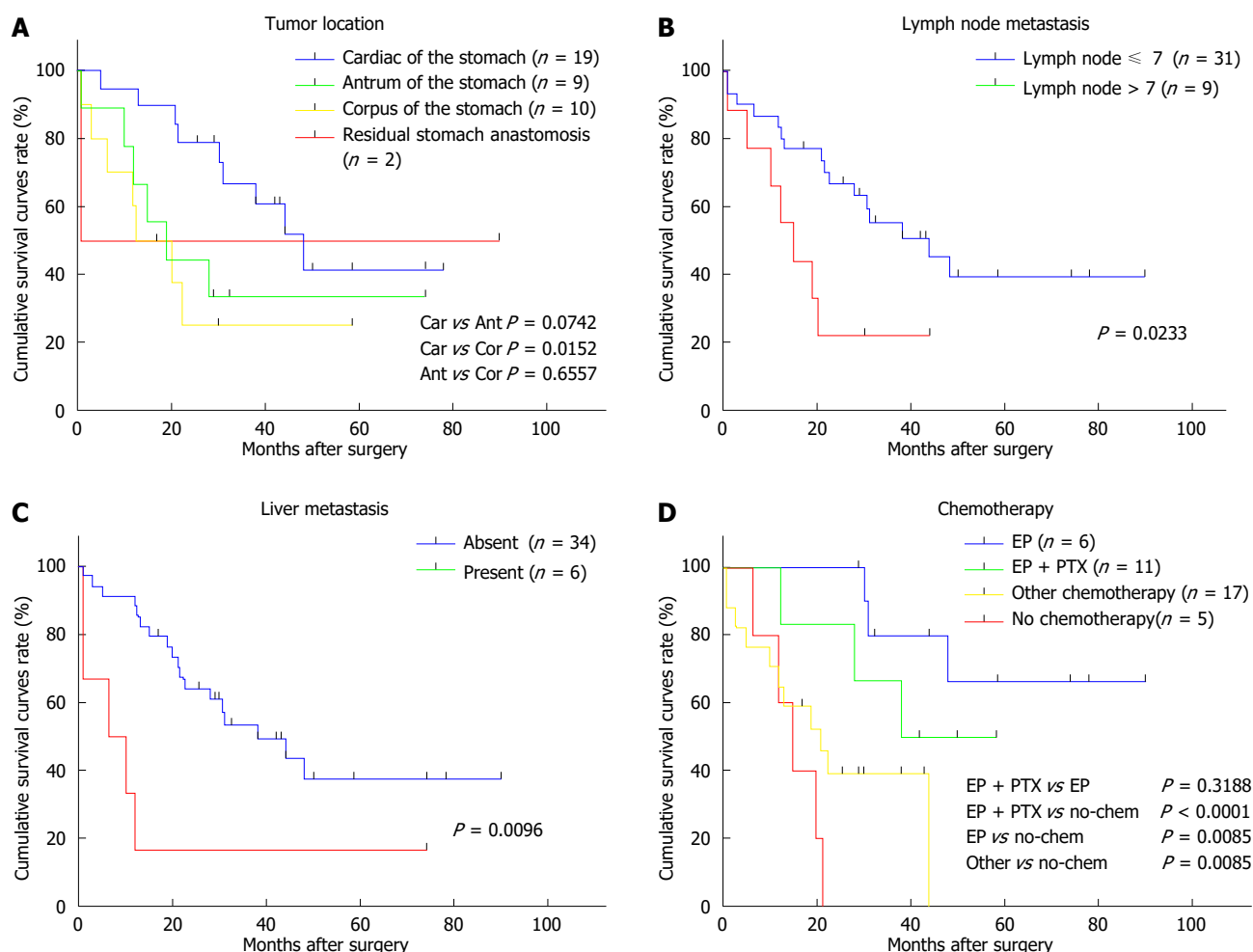
Figure 2 Survival curves of the 40 cases of gastric neuroendocrine carcinomas according to (A) tumor location, (B) lymph node metastasis number, (C) liver metastasis, (D) postoperative chemotherapy. EP: Etoposide plus cisplatin; EP + PTX: EP plus Paclitaxel.

carcinomas of the gastrointestinal tract and coined the term carcinoid. Then, for a long period, these tumors were referred to as carcinoids, even in the first WHO classification published in 1980, most of the NENs are still named carcinoids, except for endocrine tumors of the pancreas and thyroid, paragangliomas, small-cell lung carcinomas, and Merkel cell tumors of the skin[11]. Then, in 2000, the WHO classified NENs into the following categories: well-differentiated neuroendocrine tumors, well-differentiated NECs, and poorly-differentiated NECs[12]. But the term carcinoid was still used for NENs of the gastrointestinal tract; carcinoids and malignant carcinoids were used synonymously with well-differentiated neuroendocrine tumors and well-differentiated NECs, respectively.

In order to standardize the stratification and management procedures, in 2010, the WHO adopted the classification originally proposed by the European Neuroendocrine Tumor Society in 2005 and 2006[11,13,14]. According to this new WHO classification system, the term 'neuroendocrine neoplasm' is used to define all tumors comprised of neuroendocrine cells, and GEP-NENs can be categorized as NET G1 or G2, or NEC G3. This grading system used both proliferation-based grading and histopathological diagnostic criteria. Meanwhile, the TNM classification was also introduced. However, recently many studies have revealed that the G3 category might be composed of two different entities: a group of well differentiated NETs with highly proliferation and a group of poorly differentiated NECs, including small cell carcinomas and large cell NECs. These two entities exhibit different mitotic rate, Ki67 index, response to platinum-based chemotherapy and prognosis[9,15-17]. In this study, all the 43 patients were poorly differentiated NECs with Ki67 > 60%. Among which, there are 39 small cell carcinomas and 4 large cell NECs. And our investigation suggested that there is no difference in survival between these two subtypes, which coincided with the previous study[4,18,19].

The present study examined one of the sizable series of G-NECs, all of which met the criteria defined by the current WHO classification. The patient characteristics, including a male predominance and a median age of 62 years, were similar to those presented in previous reports[19,20]. NECs can occur in almost every site throughout the body, also they can originate from each part of the stomach. G-NECs usually arose in the upper third of stomach[19]. In our study, nearly

half (48.84%) of these tumors were located in the cardiac region of the stomach. And there seems to be some difference in survival among tumor location. By analysis, we found patients with tumor located in the cardiac region of the stomach have a median survival of 48.0 mo, gastric corpus 16.25 mo, gastric antrum 19.0 mo, and residual stomach anastomosis 45.5 mo, but there was only statistic difference between cardiac region and corpus of the stomach.

Depending on the presence or absence of characteristic hormonal syndromes, NENs can be classified as functioning or nonfunctioning. Functioning NENs have the ability to produce and secrete certain hormones, such as insulin, gastrin, vasoactive intestinal polypeptide, histamine, bradykinin, 5-hydroxytryptamine, and substance P, causing hypoglycemia, diarrhea, palpitation, tachycardia, anxiety, sweating, flushing, and so on[21]. But most GEP-NENs are clinically silent. Due to the absence of easily observable symptoms, non-functioning NENs are less likely to be detected early, presenting late with large primary tumors and advanced disease. This approach is also supported by our data, which showed that none of these patients suffered characteristic hormonal syndromes, and 72.09% of such tumors were locally metastasized and 13.95% were liver metastasized when diagnosed. And patients with liver metastasis and more than 7 lymph node metastasis had a poor prognosis. However, nonfunctioning NENs may release bioactive amines at subclinical levels, causing nonspecific symptoms such as increased tumor mass and other under-recognized syndromes[22].

Standard therapy is still lacking for GEP-NENs, because of the rarity, complexity, heterogeneity, and poor understanding of this disease. Since they are a group of heterogeneous tumors, the treatment of GEP-NENs should be highly individualized, based on the diverse range of tumor burden and symptoms.

Until now, surgery has been the primary and most important treatment for GEP-NENs, and is also the only possible curative treatment[2]. For grade 1-2 GEP-NENs without extensive local invasion and advanced distant metastases, surgery is the best option[23]. In the case of G-NECs, it is generally accepted that, when possible, surgical resection of the primary tumors and metastases is the most beneficial treatment, and it is the only possible cure approach[24]. Previous research has shown that R0 resection of metastases is a potential curative option[2]. And in our study, one patient with resected liver metastasis has survived for more than 74 mo with no recurrence.

Palliative surgery, which can be performed before or after medical treatment, also plays an important role in treating unresectable metastases by debulking or bypassing to make medical treatment more effective or to decrease the secretion of bioactive hormones[2,22]. Other therapies, such as embolization/chemoembolization, radiofrequency ablation, and liver transplantation, should also be considered in selected patients with disseminated liver metastases[24].

For G-NECs, as a group of poorly-differentiated tumors, only radical surgery is not sufficient, medical treatments should also be applied. It has been reported by many studies that surgery alone is rarely curative, even for those with apparently localized disease[25]. Currently available medical treatments include chemotherapeutics, biotherapeutics, targeting agents, and peptide-receptor radionuclide therapy.

It has been reported that additional systemic chemotherapy can improve the survival in patients with NECs[16,26]. In 1991, Moertel *et al*[27] reported the favorable response of EP in treating GEP-NECs, since then the EP regimen has been recommended as the first-line treatment. In our study, six patients received 2-9 cycles (mean: 6 cycles) EP regimen treatment after surgery, and got a median survival of 48.25 mo significantly longer than those who didn't receive chemotherapy (n = 5, median survival: 15.0 mo). As we all know, the short-response-time of the EP regimen in treating lung small cell NECs is obvious. So many other different chemotherapeutics have been explored in the past few years[28,29], such as the 3-drug regimen (EP + PTX). In a past report[30], this 3-drug regimen did not improve the median survival. In our study, 11 patients who received this treatment acquired the best prognosis [median survival: undefined (8 alive and 3 dead)], but it didn't reach a significant value compared with those who received EP regimen (P = 0.3188).

Gimeracil and Oteracil Potassium capsules have been reported to be an effective adjuvant treatment for East Asian patients with locally advanced gastric cancer[31]. Koide *et al*[32] reported a case of G-NEC with lymphatic metastasis who received Gimeracil and Oteracil Potassium Capsule and cisplatin chemotherapy after total gastrectomy and achieved a PFS of 45 mo. The authors of this study retrospectively reviewed the charts of 11 patients (stage Ⅲ or Ⅳ) who got Gimeracil and Oteracil Potassium Capsule chemotherapy after surgery, and reported that 4 of them survived for more than 2 years. However, in our study, 3 patients (2 stage Ⅲ, 1 stage Ⅳ) merely received postoperative Gimeracil and Oteracil Potassium Capsule chemotherapy and survived for an average of only 10.0 mo.

GEP-NENs express multiple somatostatin receptors, making them potential therapeutic targets for somatostatin. Somatostatin analogs, which have proved effective in controlling clinical syndromes caused by hormone production, were once thought to be ineffective in treating nonfunctioning NENs. Recently, the role of antiproliferative treatments have been expanding in treating both functioning and nonfunctioning tumors[33-35]. These treatments have been found to be well tolerated and safe, with mild adverse events and high tolerability. And, with the availability of long-acting somatostatin analogs, requiring monthly injections only, they have become even more convenient and more acceptable to patients. In our study, one patient with resected liver metastasis, received postoperative

Capecitabine plus Oxaliplatin and Paclitaxel systemic chemotherapy systemic chemotherapy plus 2-years octreotide LAR treatment, and has survived for 74 mo with no recurrence. It seems octreotide LAR might be a good maintenance drug[36]. For those patients who develop resistance to analogs, radionuclide-labeled somatostatin can be an alternative option[37].

Because of the limited efficacy of these traditional treatments, a lot of newer agents, such as sunitinib, everolimus, sorafenib, and bevacizumab are being tested in GEP-NEN[38-40]. Although these new agents have shown to be effective in stabilizing the tumors, it is too early to draw a conclusion regarding their efficacy until they have been tested in randomized trials.

It should also be addressed that, although several different medical treatment options are currently available, these treatments are limited by low (30%-40%) response rates, and by the fact that they are effective only in a subpopulation of patients and only for limited periods of time[23,24].

The incidence of G-NENs has been increasing in the past few decades, and during that time, significant advances have been made in their diagnosis and treatment. However, the understanding of G-NECs is still limited, and most of them are diagnosed too late, leading to a poor prognosis. Therefore, there is a pressing need for further research, physician education, and identification of molecular markers and improved imaging modalities to enable early diagnosis. And, to further develop more effective treatment strategies, more clinical trials should be conducted. Finally, the limitations of this study should be acknowledged. There might be some bias in the multivariable prognosis analysis because of the small sample size.

COMMENTS

Background
Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are a group of pathologically and clinically heterogeneous tumors with benign to high-grade malignant behavior. In the past several decades, the incidence of GEP-NENs has increased over time. However, there seemed to be no improvement in outcomes, because of our limited understanding of this disease and a lack of uniform pathology classification and staging system. In 2010, the World Health Organization (WHO) issued a new classification. According to this classification, GEP-NENs can be categorized as neuroendocrine tumor (NET) G1 or NET G2, or neuroendocrine carcinoma (NEC) G3. Gastric NECs (G-NECs) are a group of poorly differentiated tumors with high-grade malignancy. Here, the authors report the medical records of 43 patients with G-NECs that met the definition of the updated (2010) WHO classification.

Research frontiers
The understanding of G-NECs is still limited, and most of them are diagnosed too late, leading to a poor prognosis. The results of this study contribute to provide more information about the potential diagnostic factors and treatment regimens for G-NECs.

Innovations and breakthroughs
G-NECs are mostly nonfunctioning, which lead to a delay in detection. Local and/or distant metastases were noticed in most patients when diagnosed, and they required postoperative medical treatment. Adjuvant etoposide, cisplatin plus Paclitaxel systemic chemotherapy is recommended for these patients.

Applications
This study suggests that survival after surgery was better in patients with tumor located in the cardiac region of the stomach, less than 7 lymph nodes metastasis and no liver metastasis. And patients of G-NECs will benefit from adjuvant etoposide, cisplatin plus Paclitaxel systemic chemotherapy.

Terminology
NENs are a group of pathologically and clinically heterogeneous tumors with benign to high-grade malignant behavior originating from the diffuse neuroendocrine cell system. They can occur in almost every site throughout the body, especially in the lung, small intestine, rectum, pancreas, stomach, cecum, colon, appendix, and thymus. And more than half of extra-pulmonary NENs occur in digestive tract.

Peer-review
This manuscript has shown clinicopathological features of 43 patients with neuroendocrine carcinoma of the stomach. The authors provide important information related to prognosis and treatment of NECs. The study was well-designed and the manuscript was well-organized and well-write.

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