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Review Article

Management of primary gastric small cell carcinoma in China

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Abstract: Background: Primary gastric small cell carcinomas (GSCCs) are increasingly identified by endoscopy, and account for 15-20% of all gastric neuroendocrine tumors (NETs). GSCCs have the worst prognosis with the highest rate of metastases. Purpose: To provide useful information for clinicians and researchers to better manage patients with GSCC, we studied the clinical features of GSCC and explored the corresponding therapies and prognosis. Methods: A literature search was conducted through PUBMED, EMBASE, CNKI and WanFang Databases using search terms "stomach" or "gastric" and "small cell carcinoma" or "poorly differentiated neuroendocrine carcinoma", for the period 1999 to 2012. And the cases reported were all from China. Relevant articles were identified through manual review. The reference lists of these articles were reviewed to include further appropriate articles. Results: Two hundred and five eligible cases were analyzed. The median age of patients was 62 years, with a male-to-female ratio of 5.4:1. Of the tumors, 53.17% were located in the upper stomach, 25.37% in the mid, 18.54% in the distal stomach, the remaining 2.93% were found in the total stomach. The mean size was 68mm in maximum diameter, with a range of 15-150 mm. Of the one hundred and thirty-five patients, fifty appeared to be pure GSCCs, eighty-five were mixed. The median overall survival time of 195 patients was 18.50 months. The 1-, 2-, and 5-year average survival rates of 142 patients were 66.75%, 37.13%, and 20.15%, respectively. Conclusions: GSCC is a rare tumor and it is notoriously aggressive with a strong propensity for both regional and distant spread. Therapies including surgical resection, chemotherapy, and local radiotherapy, by itself or in combination with other treatment, have been used to treat GSCCs in China. To identify the most effective treatment modalities for GSCCs, we still need prospective, multicenter, randomized clinical researches.

Keywords: Small cell carcinoma, poorly differentiated neuroendocrine carcinoma, stomach, gastric

Introduction

Neuroendocrine tumors(NETs) are heterogeneous neoplasms, originating from different cells distributed in a large variety of anatomical locations throughout the body that share a common neuroendocrine phenotype [1]. Small cell carcinoma (SCC) is a group of the most aggressive and highly malignant NETs composed of small round or egg-shaped cells with little cytoplasm, which are found in various locations, but arises most frequently from the lung. Primary gastric small cell carcinoma (GSCC), first described in 1976, is an extremely rare neuroendocrine tumor that represents less than 0.1% of all gastric cancers [2, 3] and meanwhile accounts for 15-20% of all gastric NETs [4]. However, GSCC is notoriously aggressive with a strong propensity for both regional and distant spread [5, 6]. Prognosis is very poor for the patients without treatment, even just localized disease [7]. Due to the rareness of this disease, the majority of publications were only sporadic case-reports in the literature. It is for that very reason that the treatment protocols of GSCC have not been well established.

In recent years, the incidence of primary GSCCs in China has been increasing gradually because of the development of pathologically diagnostic techniques. In this report, we retrospectively analyzed the pathological characteristics, the clinical characteristics, the treatments and prognosis of GSCC.

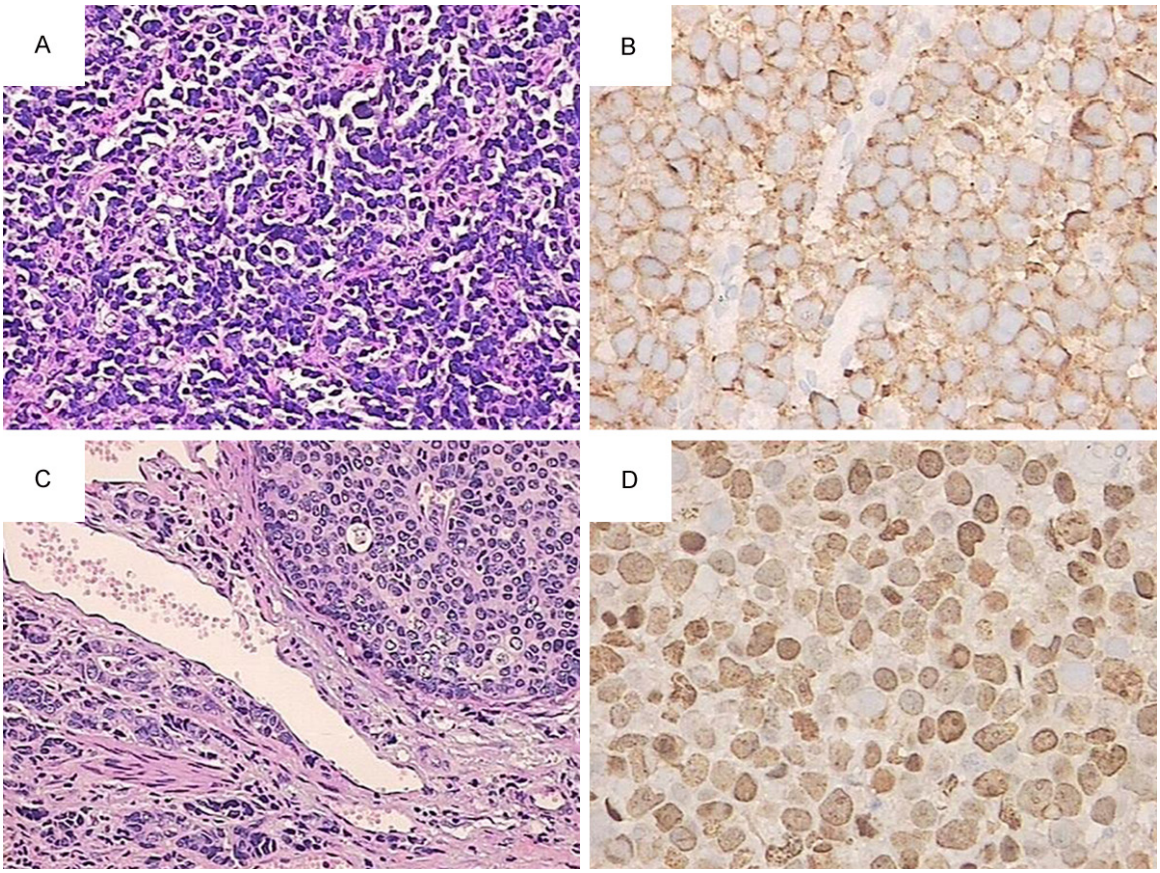

Figure 1. A. Histopathological appearance of gastric small cell carcinoma in the pure type; B. Histopathological appearance of adenocarcinoma and small cell carcinoma components in the mixed type; C. Immunohistochemistry for synaptophysin of gastric small cell carcinoma showing diffuse positivity; D. The gastric small cell carcinoma component was strongly positive for Ki67. (A, H&E staining, original magnification 10×20; B, The mixed type 10×20; C, Synaptophysin, 10×40; D, Ki67, 10×40).

Materials and methods

We systematically reviewed the Chinese- and English-language literature for the studies with primary data on GSCCs in China. We searched for publications in the Chinese medical literature using China National Knowledge Infrastructure (CNKI) and WanFang Databases that are two of the primary digital libraries providing most comprehensive access to full-text documents of publications in China. Using PUBMED and EMBASE, we performed additional searches for English-language literature, in which the patients reported were all from China. The original articles were identified with the keywords and topics related to “stomach” or “gastric” and “small cell carcinoma” or “poorly differentiated neuroendocrine carcinoma”, published during the period from 1999 to 2012. When cases were reported more than once, data of these cases from the most recent publication were used to analyze. All eligible cases were extracted according to a set of recorded features including age, gender, tumor site, histology (pure or mixed), tumor staging (tumor-node-metastasis (TNM)), treatments, and follow-up. Local treatment consisted of radiotherapy and surgery, and systemic treatment consisted of adjuvant chemotherapy, neoadjuvant chemotherapy and somatostatin analogues.

The histological criteria for the diagnosis of GSCC was identical to that of pulmonary small cell carcinoma (SCLC) [8]. All eligible patients were required to have a histological diagnosis of GSCC according to the World Health Organization criteria (WHO, 6th edition). Histochemical and immunohistochemical staining were determined by argyrophilia and the direct or indirect presence of common neuroendocrine markers including NSE (neuron-specific enolase), Syn (synaptophysin), CgA (chromogr-

Table 1. Tumor clinical characteristics

Characteristics	Patients	
	Number	Percentage, %
Gender (n=205)		
Male	173	84.4%
Female	32	15.6%
Tumor length (mm) (n=200)		
Average	68	
Range	15-150	
Tumor location (n=205)		
Upper stomach	109	53.17%
Middle stomach	52	25.37%
Lower stomach	38	18.54%
Total stomach	6	2.93%
Histological component (n=135)		
Pure type	50	37.04%
Mixed type	85	62.96%
Immunological marker		
Syn	167	83.92 %
NSE	88	63.31%
CgA	91	59.09%
CD56	80	48.19%
AE1/AE3	24	37.50%
Pathological type (n=144)		
Ulcerative type	83	57.64%
Ulcer infiltrating type	26	18.06%
Protruding/Fungating type	35	24.31%
TNM staging (n=153)		
I	6	3.92%
II	19	12.42%
III	103	67.32%
IV	25	16.34%

Abbreviations: Syn = synaptophysin, NSE = neuron-specific enolase, CgA = chromogranin A, CK = cytoeratin, CD56 = lymphocyte antigen 56, AE1/AE3 = Pan cytokeratins.

anin A), CK (cytoeratin), CD56 (lymphocyte antigen 56), AE1/AE3 (Pan cytokeratins) and others.

Currently, a revised consensus guideline of classification, staging and grading of NETs was recommended by both European and North American NET Societies (ENETS and NANETs) and WHO-2010 [9]. Limited studies retrospective studies have been used to validate the criteria. However, for all we know, no such review has been done in China. Because of this reason, the tumor-node-metastasis (TNM) system (6th edition, American Join Committee on Cancer (AJCC)) was adopted in present study [10]. The choice of employing different system may depend on the management algorithms applied. Follow-up was reported in terms of time. We computed the mean standard deviation of the continuous variables, where the differences were compared using the Mann-Whitney or Kruskal-Wallis test. Overall survival was calculated as the time from diagnosis to death or the last follow-up appointment for surviving patients. Statistical analyses were performed using the Fisher's exact test by the SPSS 18.0.

Results

Patient characteristics

A total of 12 original articles on GSCC in China were published during the selected period in our study. Among these articles, there were only 9 eligible articles in which the studies covered 5 provinces and regions of China [5, 11-18], and the median time of patients collection was 12 years (range from 6 to 18.5 years).

Two hundred and five patients with gastric small cell carcinomas were admitted from these selected 9 articles. The rate of the patients with GSCC in different provinces and regions during the time period ranged from 0.10 to 0.83%, and the median rate was 0.44%. Among the 205 patients, 173 were males and 32 were females. The male-to-female ratio was 5.4:1 and the mean age was 62 years, with a range of 32-84 years. Among these 205 patients, 11 were lost to follow-up after the initial surgical operation [5, 11-18].

Pathological characteristics

GSCC's characteristics under the microscope are essentially indistinguishable from their counterparts in the lung in histological and immunohistochemical features [7, 19], which are made up of round to spindle-shaped cells with very scant cytoplasm and small-sized oval nuclei with inconspicuous nucleoli (**Figure 1A**). Thirty-one patients were diagnosed by electronic gastroscope and biopsy. Two hundred patients were further diagnosed with GSCC by postoperative histopathology and a part of patients were applied with immunohistochemical staining.

Table 2. The treatments used for GSCCs in China

Treatments	Patients	
	Number	Percentage, %
Surgery		
Radical resection	163	79.51%
Palliative operation	34	16.58%
No surgery	5	2.44%
Chemotherapy		
Adjuvant chemotherapy	136	66.34%
Neoadjuvant chemotherapy	3	1.46%
Palliative chemotherapy	3	1.46%
Radiotherapy	2	1.0%
No radiotherapy	203	99.0%
Treatment with somatostatin analogues	0	

Carcinomas containing both SCC and non-SCC elements are designated "mixed" or "combined". Approximately half of SCCs contain non-SCC elements. In previous literature reviews, the composite type accounts for 41.1-63.1% of all GSCC [3, 6], while in this study, the composite type accounts for 62.96% of all GSCC. And adenocarcinomas are the most common non-SCC elements in the GSCC (**Figure 1B**). Fifty of the tumors appeared to be pure GSCC, eighty-five were mixed, and the rest of the seventy patients did not mention this information in the articles.

Immunohistochemical staining of neuroendocrine markers, including Syn, CgA, NSE, AE1/AE3 and CD56, is usually positive [7, 20-22] (**Figure 1C**). Immunohistochemical information was available for 199 patients. Staining for the above five immunological markers (CgA, Syn, AE1/AE3, NSE and CD56) was performed on a part of the cases. Specifically, 83.92% (167/199) of the immunological reactivity of the samples were Syn, 63.31% (88/139) were NSE, 59.09% (91/154) were CgA, 48.19% (80/166) were CD56, and 37.50% (24/64) were AE1/AE3 [5, 11-18]. GSCCs had a high grade with a Ki67 (**Figure 1D**), ranging 30.0% to 95.5%, which was consistent with previous reports [22]. At present, the Ki67 index is used to determine prognosis and direct clinical management.

Tumor characteristics

Tumor characteristics were summarized in **Table 1**. In the present study, the tumor length was measured for most patients (97.6%, 200/205). The mean size, determined by endoscopy, radiological imaging, and gross measurements, was 68 mm in greatest dimension, with a range of 15-150 mm. Generally, the tumor location varied among the patients. For most patients (53.17%, 109/205), the tumors were located in the upper stomach. The tumors were found in the mid stomach for 52 patients (25.37%, 52/205), and in the distal stomach for 38 patients (18.54%, 38/205). In addition, the rest of the 6 cases with GSCC were found in the total stomach. Eighty-three of the tumors were described as ulcerative type, twenty-six as ulcer infiltrating type and thirty-five as protruding/fungating type, and the other sixty-one patients were lack of the information in this regard.

Only a small part of the patients were pathologically confirmed to be malignant gastric tumor by electronic gastroscope and biopsy before operation. As this research showed, only 31 patients (15.12%, 31/205) were histologically diagnosed with GSCC before surgery. Lots of patients often misdiagnosed as adenocarcinoma or squamous cell carcinomas before operation [13, 14, 16, 17].

Staging

Most of tumors were staged according to the tumor-node-metastasis (TNM) staging system for gastric cancer (6th edition, American Join Committee on Cancer (AJCC)), and the rests did not mention this information in the articles.

According to the AJCC TNM staging system, of 153 cases studied, there were 4 cases in stage Ib (2.61%, 4/153), 2 cases in stage I (1.31%, 2/153), 5 cases in stage IIa (3.27%, 5/153), 9 cases in stage IIb (5.88%, 9/153), 5 cases in stage II (3.27%, 5/153), 12 cases in stage IIIa (7.84%, 12/153), 41 cases in stage IIIb (26.80%, 41/153), 3 cases in stage IIIc (1.97%, 3/153), 47 cases in stage III (30.72%, 47/153), and 25 cases in stage IV (16.34%, 25/153) [5, 11, 13, 14, 16-18].

Clinical Features

We observed that the clinical features were often dominated by the advanced stage at diagnosis. Clinical symptoms of GSCC were similar

to those of patients with carcinomas in the corresponding affected organ of the stomach, and no significant specificity was seen in computerized tomography (CT) imaging and electronic gastroscope [23, 24]. Most of patients complained of upper epigastric discomfort (ranging from 47.83 to 80.00%) and/or dysphagia (ranging from 34.04 to 70.73%) as the major presenting symptoms. A large part of patients had anemia (ranging from 47.83 to 59.57%) and/or weight loss (ranging from 20.00 to 43.90%), a few patients might have anepithymia, nausea, vomiting, gastrointestinal haemorrhage and melena, etc. GSCC most often metastasizes to the liver, and patients may present with indications or symptoms related to disease metastasis. Paraneoplastic syndromes were not observed in our series. The duration of symptoms before diagnosis varied from 7 days to 13 months, with a mean time of 2.5 months.

Treatment

The standard treatment strategies for GSCC have not yet been established. Most oncologists have recommended using the same therapeutic strategies as those used for SCLC, because of the lack of adequate data, together with the apparent histological and clinical resemblance to the familiar SCLC. Modalities used to treat GSCC principally include surgery, chemotherapy, and radiotherapy [7]. Of the 205 patients studied, 200 patients received surgical resection, in which 166 patients underwent radical resection and 34 patients with palliative operation [5, 11-18]. The resection rate and radical resection rate were 97.56% (200/205) and 83.00% (166/200), respectively. Adjuvant chemotherapy was used in 136 cases, almost all of which with 2-6 courses of platinum-based combination chemotherapy, 3 cases with neoadjuvant chemotherapy, and only 2 cases with radiotherapy, respectively. Other 64 patients did not have the records of adjuvant chemoradiotherapy after surgery [5, 11-18]. 5 patients did not undergo surgery as a result of the presence of distant metastasis at diagnosis, in which 3 patients only received chemotherapy, other 2 patients did not receive any treatment [14, 16]. While the neuroendocrine features of GSCC might theoretically allow treatment with radiolabelled somatostatin analogues [7], but this approach had not been observed in this study. **Table 2** showed our detailed analysis of the treatments for GSCC patients.

Prognosis

Usually, the prognosis of patients with GSCC is dismal even for the patients with apparently localized disease on account of early metastasis after surgery [3, 25, 26]. The prognosis is much more poor for patients who do not receive any treatment, with median survival measured in weeks, and no long-term survivors [7]. Of the 205 patients, the median survival time of 195 patients was 18.50 months [5, 12-18]. The median survival time of patients with and without surgery were 46.45 months (range, 10-63 months) and 7.65 months (range, 3-26 months), respectively [14, 16]. The patients tolerating systemic chemotherapy could obtain a more long-term survival. The median survival time of patients with and without adjuvant chemotherapy were 48.5 months (range, 5.2-228 months) and 19 months (range, 4.3-19 months), respectively [5]. The 1-, 2-, and 5-year average overall survival rates of 142 patients were 66.75% (range, 47.80-77.50%), 37.13% (range, 19.10-46.30%), and 20.15% (range, 4.30-36.60%), respectively [5, 14, 16-18].

Discussion

Primary GSCC is extremely rare, poorly differentiated, and highly malignant NETs. Yet regrettably, the exact pathogenesis is remaining largely unknown. Some researchers advocated a theory in which a pluripotent stem cell may be partially differentiated into squamous cell carcinoma and partially into adenocarcinoma or small cell carcinoma because of the stimulation of different carcinogenic agent [27, 28]. Similarly, we also found that GSCC were admixed with other histologic types of carcinoma such as adenocarcinoma or squamous cell carcinoma. In our results, of the 135 patients studied, 85 were composite type. Nevertheless, some investigators suggested that SCC elements may arise as a late-stage phenomenon in the genetic progression of carcinomas [8]. In addition, it has even been suggested that inflammatory cytokine gene such as IL-1B-511 and IL-1B-31 genotype may enhance the risks of gastric cancer [29]. But now, the correlation between inflammatory cytokine gene and GSCC is not clear. So far, it is almost impossible to identify whether such factors play a role in the pathogenesis of GSCC, but more investigations into their functions is imperative.

We observed the very low preoperative diagnostic rate, in which 84.88% cases were pathologically confirmed as undifferentiated adenocarcinoma or other types by preoperative electronic gastroscope and biopsy. The following reasons may account for the misdiagnosis based on the biopsy: first of all, the small amount of tissues picked for endoscopic biopsy could be limited for the diagnosis and sometimes incur difficulties to differentiate GSCC from poorly differentiated adenocarcinoma. Secondly, in biopsy material, GSCC always becomes artificially distorted, producing the "crush" effects that frequently obscure the diagnosis [3, 7]. Consequently, resected specimens allow better evaluation of the histologic details. In addition, electron microscope, immunohistochemical and molecular findings are useful for the differential diagnosis. In the present study, we noted that the incidence for positive immunohistochemical reactivity for Syn, NSE and CD56 in GSCC were 83.92%, 63.31% and 59.09%, respectively, which was similar with previous reports [7, 21]. The existing reports regarding the role of newer imaging studies in GSCC, such as magnetic resonance imaging (MRI) and CT imaging, have rarely been described and have been non-specific. However, the available published data indicates that FDG PET/CT plays an important role in the staging and response assessment of SCC, while somatostatin-receptor scintigraphy is unlikely to provide any additional information [23].

The clinical features of GSCC with limited stage were similar to those of patients with carcinomas in the corresponding affected organ of the stomach [23, 24]. Systemic symptoms, such as anepithymia, anemia and weight loss, are common. Other presenting symptoms are site-specific. However, regardless of the precise location, epigastric discomfort, dysphagia, nausea, and melena are common. In our series, epigastric discomfort (ranging from 47.83 to 80.00%) and dysphagia (ranging from 34.04 to 70.73%) were observed in advanced patients, respectively, which were identical to the rate of gastric adenocarcinoma without significant difference. GSCC rarely secreted kinds of ectopic hormones such as vasoactive intestinal peptide, gastrin and so on [7, 30], which can result in paraneoplastic syndromes and even dominate clinical presentation. Paraneoplastic syndromes were not observed in our series. Even so, it is still necessary to evaluate paraneoplastic syndromes in the patients, especially when there is a clinical suspicion of GSCC. In clinical practice, GSCC arising from different locations of stomach shares similar pattern of spread. Most tumors are diagnosed with regional lymph node involvement and some have overt distant metastases [7]. GSCC most often metastasizes to the liver, followed by distant lymph nodes, bones, and bone morrow, and patients may present with signs or symptoms related to disease metastasis.

Currently, there were no randomized controlled trials which have been undertaken to establish the optimal therapy for GSCC because it's very hard to get adequate numbers for a quality randomized controlled trial for its lower incidence rate and limited knowledge. However, the limited data in the literature is available describing the optimal treatment of patients with GSCC. Modalities including surgical resection, systemic chemotherapy, and local radiotherapy, by itself or in combination with other treatment, have been used to treat GSCC [5, 12-18].

Current guidance advocates that all GSCC should be treated with oncological resections without considering grade and stage [22]. Surgical resection undoubtedly remains the mainstay of the potentially curative treatment, which was widely performed to treat localized disease in patients with this disease. Of the 205 patients studied, 200 patients received surgical resection. The median survival time of patients with and without surgery were 46.45 months (range, 10-63 months) and 7.65 months (range, 3-26 months), respectively [14, 16]. Similarly, several cases treated by surgery alone could obtain a mean survival of 20 months [31]. In addition, in a review of 54 patients with GSCC, 3 patients without distant metastasis survived for more than 2 years after operation with dissection of regional lymph nodes [26, 32]. Taken together, these findings indicate that surgery may be considered as a standard treatment for limited disease of GSCC.

Systemic chemotherapy is now identified as the foundation of treatment for GSCC because of the high metastasis and recurrence rate [7]. Chemotherapy had improved the median survival to a range of 6-12 months, with occasional long-term survivors [33]. Our results demonstrated that postoperative chemotherapy significantly improved survival in patients with limited stage. Adjuvant chemotherapy was

used in 136 cases, almost all of which with two to six courses of platinum-based combination chemotherapy. Amazingly, the median survival of 48.5 months (range, 5.2-228 months) observed in patients with adjuvant chemotherapy, which is much better than the 19 months (range, 4.3-19 months) for the patients without it [5]. Analogously, Koide et al. reported a patient after surgery treated with chemotherapy experienced a more than 45 months of relapse-free survival [34]. Several studies have compared different regimens of chemotherapy [26, 34-37]. Unfortunately, there were no conclusions regarding which regimen was most effective on account of the sparse number of patients. Although the effectiveness of adjuvant chemotherapy is limited, it remains one of the most important strategies for treating GSCC.

Neoadjuvant chemotherapy is a modality of chemotherapy in the pre-operative setting in patients with resectable disease, which was verified to be an effective treatment against advanced gastric adenocarcinoma [38]. In recent years, it has begun to be used in GSCC, which was deemed to a feasible treatment in some literature [5, 39, 40]. It suggested that neoadjuvant chemotherapy should be recommended as standard treatment in patients with GSCC. However, the exact role of neoadjuvant chemotherapy remained controversial. In China, the application of neoadjuvant chemotherapy in GSCC was very scarce. Of the 205 patients studied, only 3 cases received neoadjuvant chemotherapy [5, 17]. Consequently, our research could not respond to the question about the role of neoadjuvant chemotherapy in limited stage.

In China, radiotherapy which was administrated in gastric small cell carcinomas was also rare. In this study, we showed that only 2 patients accepted radiotherapy [16]. Several trials and meta-analyses have shown that radiotherapy combined chemotherapy with could improve the curative effects [7], radiotherapy could provide locoregional control and subsequent long-term survival in isolated cases [24, 41]. Yet, we are still uncertain the accurate role of radiotherapy in GSCC. The exact role of radiotherapy in administrating GSCC needs further investigation with randomized controlled trials to establish long-term efficacy.

Theoretically, somatostatin analogue was regarded as a possible treatment against GSCC because of its neuroendocrine features. Nevertheless, this strategy has not been reported in China as yet. Similar to China, this kind of treatment applied in other countries was also quite rare [7]. However, there are no randomized controlled trials to determine whether somatostatin analogue was effective treatment for GSCC at present. Therefore, more studies are needed before this approach can be recommended to treat GSCC.

In spite of the application of multimodality treatment, the overall prognosis of GSCC is universally dismal with a mortality rate of 22-30% [3, 7, 42], even for patients with early-stage tumors as a result of high malignancy and early metastasis [3, 25, 26]. It's our statistical fact that the median survival time of 195 patients was 18.50 months [5, 12-18], while some reports declared that they could obtain a mean survival of 20 months [31, 43]. The reason may be that the majority of patients in our group are late malignant tumor. Furthermore, the 1-, 2-, and 5-year average overall survival rates of 142 patients were 66.75%, 37.13% and 20.10%, respectively [5, 14, 16-18]. Collectively, our results demonstrate that the treatment of GSCC is still controversial and generally associated with a poor prognosis, which provide the impetus to develop more effective methods.

Conclusions

GSCC is a cancer characterized by high malignancy, early metastasis and poor prognosis. Normally, the most of reported cases come from East Asia where gastric cancer is more prevalent. This study is the first to summarize the cases of GSCC reported inside of China. It's difficult to conduct a randomized controlled clinical study in order to obtain the optimal therapeutic strategy because of the lower incidence rate. Though our comprehensive retrospective review cannot solve all problems, however, our results suggest that multimodal approaches may be an effective treatment for the treatment of GSCC and also disclose important aspects of the disease, such as its clinical features, its pathological features, prognosis and more. And still, prospective, multicenter, randomized clinical tests to identify the most effective treatment modalities for GSCC are warranted.

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Disclosure of conflict of interest

None.

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References

[1] Chau I, Casciano R, Willet J, Wang X and Yao JC. Quality of life, resource utilisation and health economics assessment in advanced neuroendocrine tumours: a systematic review. Eur J Cancer Care (Engl) 2013; 22: 714-725.

[2] Kim KO, Lee HY, Chun SH, Shin SJ, Kim MK, Lee KH, Hyun MS, Bae SH and Ryoo HM. Clinical overview of extrapulmonary small cell carcinoma. J Korean Med Sci 2006; 21: 833-837.

[3] Kusayanagi S, Konishi K, Miyasaka N, Sasaki K, Kurahashi T, Kaneko K, Akita Y, Yoshikawa N, Kusano M, Yamochi T, Kushima M and Mitamura K. Primary small cell carcinoma of the stomach. J Gastroenterol Hepatol 2003; 18: 743-747.

[4] Hassan MM, Phan A, Li D, Dagohoy CG, Leary C and Yao JC. Risk factors associated with neuroendocrine tumors: A U.S.-based case-control study. Int J Cancer 2008; 123: 867-873.

[5] Huang J, Zhou Y, Zhao X, Zhang H, Yuan X and Wang J. Primary small cell carcinoma of the stomach: an experience of two decades (1990-2011) in a Chinese cancer institute. J Surg Oncol 2012; 106: 994-998.

[6] Namikawa T, Kobayashi M, Okabayashi T, Ozaki S, Nakamura S, Yamashita K, Ueta H, Miyazaki J, Tamura S, Ohtsuki Y and Araki K. Primary gastric small cell carcinoma: report of a case and review of the literature. Med Mol Morphol 2005; 38: 256-261.

[7] Brenner B, Tang LH, Klimstra DS and Kelsen DP. Small-cell carcinomas of the gastrointestinal tract: a review. J Clin Oncol 2004; 22: 2730-2739.

[8] Frazier SR, Kaplan PA and Loy TS. The pathology of extrapulmonary small cell carcinoma. Semin Oncol 2007; 34: 30-38.

[9] In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO Classification of Tumours of the Digestive System. 4th edition. Lyon: International Agency for Research on Cancer; 2010. pp. 417.

[10] Greene FL, Page DL, Fleming ID, Balch CM, Haller DJ and Morrow M. AJCC Cancer Staging Manual. 6th edition. New York: Springer; 2002.

[11] Wang MH, Li KX and Wang SS. ClinIcopathologic analysis of 5 cases of stomach small cell carcinoma. Qi Lu Zhong Liu Za Zhi 1999; 6: 46-47.

[12] Guo J, Wen GY and Zhang GD. Small cell carcinoma of stomach: a clinIcopathologic study of 5 cases. Zhen Duan Bing Li Za Zhi 2005; 12: 260-262.

[13] Sun YL, Liu YW, Zhong DR and Gao WS. [Gastric small cell carcinoma: 6 cases report and review of literature]. Zhonghua Wai Ke Za Zhi 2008; 46: 756-758.

[14] Dong RZ, Shi YQ, Ye YW, Fu H and Zhao GF. [Clinicopathological and prognostic analysis of 23 poorly differentiated neuroendocrine carcinomas of the stomach]. Zhonghua Wei Chang Wai Ke Za Zhi 2010; 13: 583-586.

[15] Li C, Xia S and Zhang Y. Clinic Analysis of 47 Poorly Differentiated Neuroendocrine Carcinomas of the Stomach. Yi Xue Yan Jiu Za Zhi 2012; 41: 154-157.

[16] Huang S, Zheng ZX, Xu Q and Yuan XH. [The diagnosis, treatment and prognosis evaluation of gastric small cell carcinoma: analysis of 41 cases]. Zhonghua Wai Ke Za Zhi 2013; 51: 225-229.

[17] Liu H, Xie YB, Xu Q, Zhang JW, Tian YT, Zhao DB, Wang CF, Shan Y, Zhou ZX and Yuan XH. [Clinical analysis of 17 cases of gastric small cell carcinoma]. Zhonghua Zhong Liu Za Zhi 2013; 35: 292-294.

[18] Kou Y, Gao YB, Ma J, Yang K, Fu Q and Xie JG. [Prognostic analysis of 42 patients with gastric neuroendocrine carcinoma]. Zhonghua Wei Chang Wai Ke Za Zhi 2013; 16: 570-573.

[19] Wick MR, Weatherby RP and Weiland LH. Small cell neuroendocrine carcinoma of the colon and rectum: clinical, histologic, and ultrastructural study and immunohistochemical comparison with cloacogenic carcinoma. Hum Pathol 1987; 18: 9-21.

[20] Gaffey MJ, Mills SE and Lack EE. Neuroendocrine carcinoma of the colon and rectum. A clinicopathologic, ultrastructural, and immunohistochemical study of 24 cases. Am J Surg Pathol 1990; 14: 1010-1023.

[21] Li AF, Li AC, Hsu CY, Li WY, Hsu HS and Chen JY. Small cell carcinomas in gastrointestinal tract: immunohistochemical and clinicopathological features. J Clin Pathol 2010; 63: 620-625.

[22] Basuroy R, Srirajaskanthan R, Prachalias A, Quaglia A and Ramage JK. Review article: the investigation and management of gastric neu-

roendocrine tumours. Aliment Pharmacol Ther 2014; 39: 1071-1084.
[23] Joyce EA, Kavanagh J, Sheehy N, Beddy P and O'Keeffe SA. Imaging features of extrapulmonary small cell carcinoma. Clin Radiol 2013; 68: 953-961.
[24] Frances N, Zeichner SB, Francavilla M and Cusnir M. Gastric small-cell carcinoma found on esophagogastroduodenoscopy: a case report and literature review. Case Rep Oncol Med 2013; 2013: 475961.
[25] Kim BS, Oh ST, Yook JH and Park YS. Primary small cell carcinoma of the stomach: clinical outcomes and prognoses. Am Surg 2013; 79: e305-307.
[26] Okita NT, Kato K, Takahari D, Hirashima Y, Nakajima TE, Matsubara J, Hamaguchi T, Yamada Y, Shimada Y, Taniguchi H and Shirao K. Neuroendocrine tumors of the stomach: chemotherapy with cisplatin plus irinotecan is effective for gastric poorly-differentiated neuroendocrine carcinoma. Gastric Cancer 2011; 14: 161-165.
[27] Ho KJ, Herrera GA, Jones JM and Alexander CB. Small cell carcinoma of the esophagus: evidence for a unified histogenesis. Hum Pathol 1984; 15: 460-468.
[28] Matsui K, Kitagawa M, Miwa A, Kuroda Y and Tsuji M. Small cell carcinoma of the stomach: a clinicopathologic study of 17 cases. Am J Gastroenterol 1991; 86: 1167-1175.
[29] Feng Y, Zhang J, Dai L, Wang P, Zang J, Li Y and Wang K. Inflammatory cytokine gene polymorphisms in gastric cancer cases' and controls' family members from Chinese areas at high cancer prevalence. Cancer Lett 2008; 270: 250-259.
[30] Peng C, Shen S, Zhang X and Zou X. Limited stage small cell carcinoma of the gastrointestinal tract: a clinicopathologic and prognostic analysis of 27 cases. Rare Tumors 2013; 5: e6.
[31] Ibrahim NB, Briggs JC and Corbishley CM. Extrapulmonary oat cell carcinoma. Cancer 1984; 54: 1645-1661.
[32] Arai K and Matsuda M. Gastric small-cell carcinoma in Japan: a case report and review of the literature. Am J Clin Oncol 1998; 21: 458-461.
[33] Richards D, Davis D, Yan P and Guha S. Unusual case of small cell gastric carcinoma: case report and literature review. Dig Dis Sci 2011; 56: 951-957.
[34] Koide N, Suzuki A, Saito H, Sato T, Murakami M, Ota H and Miyagawa S. Gastric small cell carcinoma successfully treated by surgery and postoperative chemotherapy consisting of cisplatin and S-1: report of a case. Surg Today 2007; 37: 989-994.
[35] Iwamuro M, Tanaka S, Bessho A, Takahashi H, Ohta T, Takada R and Murakami I. Two cases of primary small cell carcinoma of the stomach. Acta Med Okayama 2009; 63: 293-298.
[36] Cioppa T, Marrelli D, Neri A, Caruso S, Pedrazzani C, Malagnino V, Pinto E and Roviello F. A case of small-cell gastric carcinoma with an adenocarcinoma component and hepatic metastases: treatment with systemic and intrahepatic chemotherapy. Eur J Cancer Care (Engl) 2007; 16: 453-457.
[37] Nakamura Y, Otani S, Otaka M, Shimada T, Takahashi S, Saito M, Takahashi T, Komatsu M, Suzuki T, Okubo S, Hayashi M and Sasano H. Gastric small cell carcinoma with marked response to neoadjuvant chemotherapy. Int J Clin Oncol 2005; 10: 348-352.
[38] Boku N, Ohtsu A, Shimada Y, Shirao K, Seki S, Saito H, Sakata Y and Hyodo I. Phase II study of a combination of irinotecan and cisplatin against metastatic gastric cancer. J Clin Oncol 1999; 17: 319-323.
[39] Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ and Participants MT. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355: 11-20.
[40] Onoyama H, Iwasaki Y, Ohashi M, Iwanaga T, Ohinata R, Maeda Y, Omuro Y, Sasaki E, Shimoyama T and Tateishi Y. [A case of gastric neuroendocrine cell carcinoma successfully treated by neoadjuvant chemotherapy]. Gan To Kagaku Ryoho 2011; 38: 2131-2133.
[41] Brenner B, Tang LH, Shia J, Klimstra DS and Kelsen DP. Small cell carcinomas of the gastrointestinal tract: clinicopathological features and treatment approach. Semin Oncol 2007; 34: 43-50.
[42] Rappel S, Altendorf-Hofmann A and Stolte M. Prognosis of gastric carcinoid tumours. Digestion 1995; 56: 455-462.
[43] Matsui K, Jin XM, Kitagawa M and Miwa A. Clinicopathologic features of neuroendocrine carcinomas of the stomach: appraisal of small cell and large cell variants. Arch Pathol Lab Med 1998; 122: 1010-1017.