Limited stage small cell carcinoma of the gastrointestinal tract: a clinicopathologic and prognostic analysis of 27 cases

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Abstract

Small cell carcinoma of the gastrointestinal tract is a rare and aggressive neuroendocrine tumor. This study aims to analyze the clinical characteristics and potential prognostic factors for patients with limited stage small cell carcinoma of the gastrointestinal tract. The records of 27 patients with limited stage small cell carcinoma of the gastrointestinal tract, who all received surgery with lymphadenectomy, were retrieved and analyzed retrospectively. The median age of patients was 60 years old (range 38-79). The primary locations of tumor were the esophagus (74.1%) and stomach (14.8%). The rate of preoperative accurate diagnosis (16.7%) was low for small cell carcinoma of the esophagus and stomach. 40.7% of all the patients had regional lymph node metastases. Five patients underwent surgery alone, and the other 22 were treated with surgery + postoperative chemotherapy. All patients had disease progression or recurrence. The overall median survival time was 10 months and the 1-year survival rate was 37.0%. Patients who received postoperative chemotherapy had a median survival time of 12 months, which was superior to the 5-month survival of for those who only had surgery (P<0.0001). TNM stage (P=0.02) and postoperative chemotherapy (P<0.0001) were considered as two prognostic factors in univariate analysis. Postoperative chemotherapy was a significant independent prognostic factor in multivariate analysis (P=0.01). The prognosis for patients with limited stage small cell carcinoma of the gastrointestinal tract remains dismal, however, postoperative chemotherapy may have the potential to improve the outcome for these patients.

Introduction

Small cell carcinoma (SCC) is a rare aggressive malignant neuroendocrine tumor composed of small round or egg-shaped cells with little cytoplasm. The most common site of SCC is lung. In 1930, extrapulmonary SCC was first described by Duguid and Kennedy.[1] Since then, cases of SCC have been reported in almost all sites of the body, including the gastrointestinal tract (GIT),[2] head and neck,[3] urinary tract,[4] and genital system.[5]

SCC of the GIT occurs infrequently. Approximately 1000 cases have been reported in the English literature with the estimated prevalence of 0.1% to 1% of all gastrointestinal tumors.[6] SCC can originate throughout the GIT, with the esophagus frequently involved. Early sporadic data have indicated that SCC arising from different digestive locations has similar biological behavior, including clinical presentation and pattern of metastasis, which suggests that SCC of the GIT could be regarded and treated as one clinical entity.[2] Regrettably, overall information about SCC of the GIT is limited due to its rarity and the fact that most reports focused on a particular location within the GIT. Currently, its clinicopathological characteristics and standard treatment are far from being well established. Especially in the setting of limited stage SCC of the GIT, early accurate diagnosis is challenging and the role of surgery is still controversial. Some reports suggested that surgical resection of limited stage SCC could result not only in a significant locoregional control but also in long-term disease-free survival.[7,8] However, other data indicated that patients treated with surgery alone had rapid systemic recurrence.[9,10]

Therefore, this retrospective study was performed to analyze the clinical characteristics and potential prognostic factors for patients with clinically limited stage SCC of the GIT.

Materials and Methods

We reviewed the records of 27 consecutive patients with limited stage SCC of the GIT diagnosed histologically, who underwent intended surgery with regional lymphadenectomy in the Affiliated Drum Tower Hospital of Nanjing University Medical School (Nanjing, China) from March 2006 to August 2011. The following data were collected for each patient: demographic data, presenting symptoms, methods of tumor diagnosis, staging procedures, pathologic findings, types of treatment, and survival time. Differential diagnoses were made immuohistochemically by using antibodies chromogranin A, synaptophysin, neuron-specific enolase (NSE) and cluster differentiation 56 (CD56). The histological and immunochemical diagnosis of SCC was confirmed by two independent pathologists. Staging work-up included computed tomography (CT) scan of the chest, abdomen and pelvis. Other modalities included endoscopic ultrasound (EUS) and magnetic resonance imaging. Tumors were staged according to the 2002 American Joint Committee on Cancer (AJCC) TNM staging system for each affected organ and Veterans' Administration Lung Study Group (VALSG) criteria. The latter consists of two staging categories: limited and extensive disease. Limited disease is defined as a tumor confined to a localized anatomic region such as any single organ (e.g. the esophagus, stomach, colon, gallbladder, and pancreas), with or without regional lymph node involvement. Extensive disease is defined as a tumor spread beyond any localized anatomic region. Survival time was defined as the time from the date of the end of treatment to death or the last follow-up visit. All patients gave informed consents prior to gastroscopy, surgery, or chemotherapy. This study was approved by the Ethics Committee of Drum Tower Hospital.

Statistical analysis was performed using SPSS 11.5 software (SPSS Inc., Chicago, IL, USA). The impact of clinical and pathologic risk factors on survival was evaluated using Kaplan-Meier life table analyses and log-rank

tests. The independent prognostic factors were evaluated using Cox's hazard regression model. All tests were two-tailed and a P value <0.05 was considered significant.

Results

Patient's characteristics

Twenty-seven patients (18 men and 9 women) with limited stage SCC of the GIT accounted for 0.2% of all patients with digestive malignancies treated at our hospital during the study period. The clinical characteristics are summarized in Table 1. The median age was 60 years (range 38-79). The common symptoms were dysphagia (51.9%), loss of appetite (40%) and jaundice (7.4%). Paraneoplastic syndromes were not observed in our series. The most common primary sites were the esophagus (74.1%), followed by the stomach (14.8%). The average tumor length was 4.5 cm (range 0.2-14).

According to the TNM classifications, 10 cases were stage I, 10 cases were stage II, and 7 cases were stage III. Of the 27 patients, 40.7% (11/27) postoperatively had lymph node metastasis and 63.0% (17/27) had lymphatic vessel invasion.

Diagnostic investigations

Primary SCCs of the lung were excluded in all the patients based on the CT scans of the chest. Twenty-four patients (20 esophagus, 4 stomach) underwent gastroscopic examinations and were biopsied. Among 20 esophagus SCC, 50% were located in the lower third of the esophagus, 40% were in the middle, and only 10% were in the upper third. In terms of endoscopic appearance, 15 were classified as ulcerative type, 3 were mushroom type, and 2 were submucosal protruded type (Figure 1A). Interestingly, in one of the submucosal SCCs of the esophagus, a patch-like erosion was observed at 24-28 cm (6:00-7:00 position) before staining, and a large irregular unstained area was present near the tumor after Lugol's iodine staining (Figure 1B and C). Three patients (2 esophagus, 1 stomach) preoperatively underwent endoscopic ultrasound (EUS) examinations that exhibited homogeneous hypoechoic or isoechoic masses with regular borders originating from submucosal layer or muscularis propria, which were initially mistaken as granular cell tumors (Figure 1D) or stromal tumors. Only 4 (16.7%) biopsy specimens yielded a positive diagnosis for SCC, 8 (33.3%) were misclassified as undifferentiated adenocarcinoma, 5 (20.8%) were interpreted as squamous carcinoma, 4 (16.7%) were displayed as epithelial tumors, and 3 (12.5%) were considered as reactive or

nonneoplastic. The remaining 3 cases (1 pancreas, 1 colon, and 1 gallbladder), all of whom received contrast-enhanced CT for diagnosis, were not biopsied preoperatively. In the case of SCC in pancreas, CT displayed a large, heterogeneous, and marked enhancing mass at the pancreatic head (Figure 2A and B).

Histology and immunohistochemistry

Histology in SCC of the GIT was similar to classical SCC: spindle-shaped cells with scanty cytoplasm and hyperchromatic nuclei. Twenty-five cases (92.6%) had pure SCC, 1 (3.7%) case of gallbladder had mixed type glandular adenocarcinoma differentiation (Figure 3A),
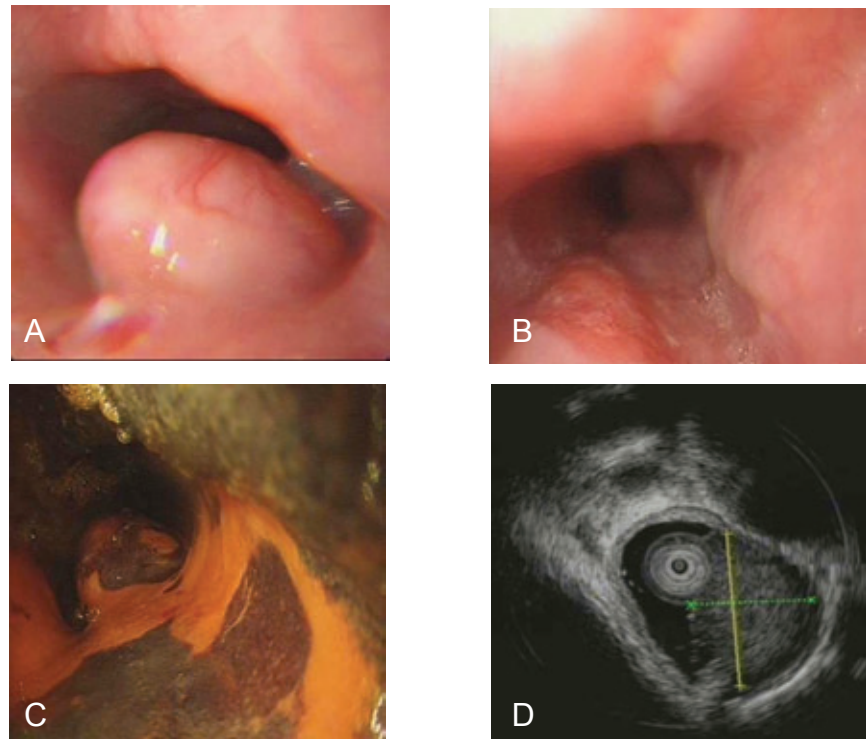

Figure 1. Endoscopic views of the small cell carcinoma of esophagus. A) A submucosal elevated lesion (1.5x1.5 cm) covered with normal esophageal mucosa at 25 cm in esophagus; B) a patch-like erosion is observed at 24-28 cm (6:00-7:00 position) in esophagus before staining; C) a large irregular unstained area at 24-28 cm in esophagus after Lugol's iodine staining; D) a homogeneous, isoechoic mass (1.0x1.1 cm²) with a regular border originating from submucosal layer in esophagus, which is diagnosed as a granular cell tumor by EUS.

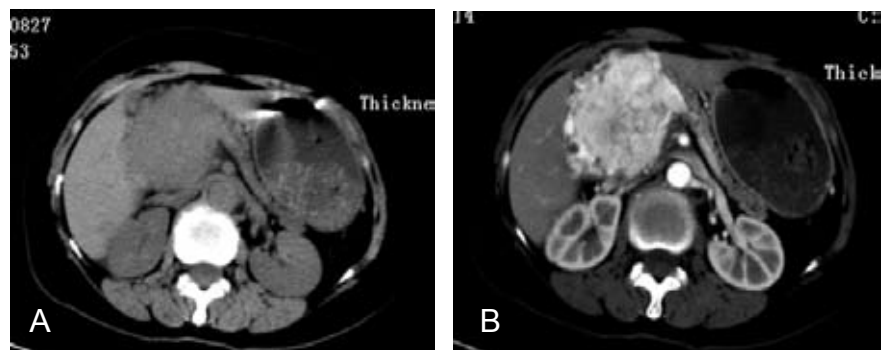Figure 2. Small cell carcinoma of the pancreas in a 56-year-old man. A) Computed tomography (CT) scanning demonstrates a 5.0x3.8 cm mass at the head of the pancreas, with atrophic pancreatic parenchyma and main pancreatic duct dilation. B) Contrast-enhanced CT scanning shows a marked, heterogeneous enhancement in both peripheral and central portion of the tumor at 30s after administration of contrast medium.

and 1 (3.7%) case of esophagus had mixed type glandular squamous differentiation.

All surgical specimens were immunohisto-chemically stained for epithelial and neuroendocrine markers. Of all cases, 20 (74.1%) were synaptophysin positive (Figure 3B), 14 (51.9%) were chromogranin A positive, 12 (44.4%) were CD56 positive, and 10 (37.0%) were NSE positive.

Treatment and prognosis

All of the 27 patients underwent radical surgery and in 2 cases (1 esophagus and 1 stomach) local resection was first performed by thoracoscopy or gastroscopy. Among all the patients undergoing operations, five were treated with surgery alone and the other 22 were treated with surgery + postoperative chemotherapy. Of the 5 patients undergoing surgery alone, three declined further treatment, and the other two were not candidates for chemotherapy because of poor performance status. Among those who received chemotherapy, twelve cases received etoposide combined with cisplatin (EP), and the other 10 cases received a combined regimen of cyclophosphamide + doxorubicin + cisplatin

(CAP). All 27 patients died and none was lost to follow-up. The median survival was 10 months. The 6- and 12-month survival rates for the whole group were 70.4% and 37.0%, respectively (Figure 4A). In view of different primary sites, the median survival time for patients

with SCC of the esophagus was 12 months followed by that of SCC of the stomach (median survival time, 11 months). There was no statistically significant difference in survival time among patients with SCC of these different locations (P=0.30). With regard to different
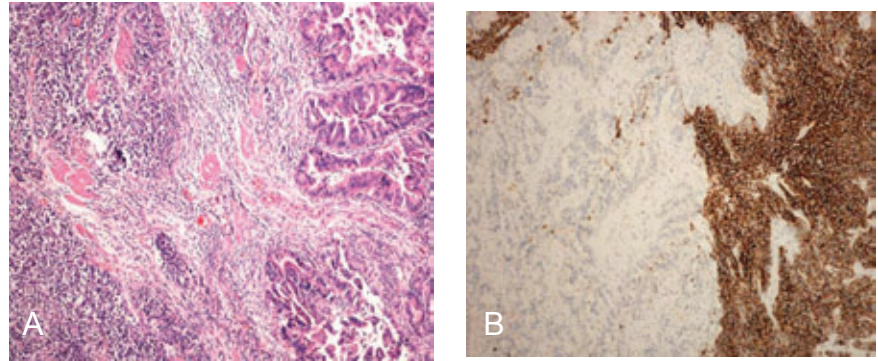

Figure 3. Mixed small cell adenocarcinoma of the gallbladder. A) Haematoxylin &Eosin stained sections shows small, round cells with scanty cytoplasm, granular nuclear chromatin and inconspicuous nucleoli (left), which is combined with components of adenocarcinoma (right) (Magnification x100); B) immunohistochemical staining for synaptophysin, which is positive in the small cell carcinoma area and negative in the adenocarcinoma area.

Table 1. Clinical characteristics of patients with small cell carcinoma of the gastrointestinal tract (N=27).

Characteristic	No. in group (% of entire group)
Sex	
Male	18 (66.7%)
Female	9 (33.3%)
Location	
Esophagus	20 (74.1%)
Stomach	4 (14.8%)
Colon	1 (3.7%)
Gallbladder	1 (3.7%)
Pancreas	1 (3.7%)
Colon	1 (3.7%)
Gallbladder	1 (3.7%)
Pancreas	1 (3.7%)
Histological homology	
Pure	25 (92.6)
Mixed	2 (7.4)
Pure	25 (92.6%)
Mixed	2 (7.4%)
TNM	
I	10 (37.0%)
II	10 (37.0%)
III	7 (25.9%)
Lymph node involvement	
Yes	11 (40.7%)
No	16 (59.3%)
Lymphatic vessel invasion	
Yes	17 (63.0%)
No	10 (37.0%)
Therapy	
Surgery	5 (18.5%)
Surgery + chemotherapy	22 (81.5%)

Table 2. Univariate analysis of survival on clinical and pathologic factors.

Variables	Median survival (month)	Survival rate (%) 6-month	Survival rate (%) 1-year	P value
Gender				
Male	9	66.7	27.8	0.09
Female	13	77.8	55.6	
Age (year)				
<60	12	76.9	30.8	0.86
≥60	8	64.3	42.9	
Location				
Esophagus	12	75	40	0.30
Stomach	11	75	25	
Colon	-	-	-	
Gallbladder	-	-	-	
Pancreas	-	-	-	
Tumor length (cm)				
<4.5	12	84.6	46.2	0.14
≥4.5	8	57.1	28.6	
Histological homology				
Pure	12	76	40	0.07
Mixed	6	0	-	
TNM stage				
I	13	90	60	0.02
II	12	70	40	
III	6	42.9	0	
Lymph node involvement				
Yes	8	54.6	27.3	0.41
No	12	81.3	43.8	
Lymphatic vessel invasion				
Yes	10	58.8	29.4	0.50
No	12.5	90	50	
Therapy				
Surgery	5	0	0	<0.0001
Surgery + chemotherapy	12	86.4	45.5	

therapeutic options, the median survival time for patients who received surgery alone was 5.0 months, with a 6-month survival rate of 0%. For patients undergoing surgery + postoperative chemotherapy, the median survival time was 12 months, with a 6-month survival rate of 86.4% and a 12-month survival rate of 50% (Figure 4B). Furthermore, there was a statistically significant difference in survival between surgery alone versus surgery + postoperative chemotherapy (P<0.0001). Also, there was no significant difference in the median survivals for the cases with EP and with CAP (12 *vs* 11 months, P=0.26). Univariate analyses revealed that TNM stage and postoperative chemotherapy correlated with the outcome of patients (Table 2). Multivariate analysis indicated that postoperative chemotherapy was a significant independent prognostic factor for overall survival [Hazard ratio, 0.43; 95% CI (0.004-0.49); P=0.01] (Table 3), which suggested that the patients who underwent postoperative chemotherapy had a better prognosis. In addition, all the patients had disease progression despite multimodal therapy during the follow-up, including 7 local recurrences and 20 distant metastasis. The most frequent sites of metastasis were as follows: lymph node (45%), liver (40%), lung (10%), and bone (5%).

Discussion

SCC of the GIT is a kind of rare and highly aggressive malignancy; however, the exact pathogenesis is remaining largely unknown. Ho *et al.* suggested that SCC might be of endodermal origin derived from a pluripotent stem cell, which might have differentiated into mucin or keratin producing cells.[11] This suggestion is supported by the findings of Chen and Matsui.[12,13] Similarly, our study also indicates that SCC of the esophagus and gallbladder are admixed with other histologic types of carcinoma such as adenocarcinoma or squamous cell carcinoma. Moreover, in one case with SCC of the esophagus, Lugol's iodine staining exhibited a clearly unstained area near the tumor, and biopsies revealed moderate dysplasia. Maitra *et al.* have described that dysplastic epithelium was present in gallbladder SCC.[14] Burke *et al.* found that overlying adenomas were present in 45% of SCC of the large intestine.[15] In addition, a few genetic and molecular alternations have been recorded, including the identification of high proliferative activity, prevalence of p53 overexpression, Rb loss, telomerase activation and k-ras mutations.[14,16-18] However, these genetic and molecular data are only derived from SCC of the esophagus. To date, it is unclear whether such factors play a role in the pathogenesis of SCC of the GIT, but further investigations into their functions is warranted.

Demographically, the clinical features of our patients with limited stage SCC of the GIT are similar to those of patients with carcinomas in the corresponding affected organ of the GIT. Similar to the findings of Brenner *et al*,[2] most of our patients were men with the median age of 60 years. The most common primary location of limited stage SCC of the GIT is the esophagus. Of note, several reports have addressed that SCC of the GIT rarely secretes various ectopic hormones such as vasoactive intestinal peptide, gastrin, calcitonin, adrenocorticotropic hormone and antidiuretic hormone,[19-23] which can result in paraneoplastic syndromes and even dominate clinical presentation. Our series did not exhibit clinical signs of paraneoplastic syndromes, so we did not assess these hormone levels. In clinical practice, it is nevertheless necessary to evaluate paraneoplastic syndromes in the patients especially when there is a clinical suspicion of SCC of the GIT.

Grossly, most endoscopic and radiological features of limited stage SCC of the GIT are identical to those of other carcinomas of the corresponding sites. Our study reveals that two esophageal SCCs and one gastric SCC were submucosal tumors. Further EUS examinations found homogeneous hypoechoic or isoechoic solid masses with clear margins arising from the submucosal layer or muscularis propria. These masses were misclassified as granular cell tumors or stromal tumors by EUS. This phenomenon might be caused by rapid proliferation of the tumor into the submucosal layer. In our case of SCC of the pancreas, the mass was heterogeneously enhanced by contrast enhanced CT, as reported by Ichikawa *et al.*[24] and Namieno T *et al.*[25] Generally, the adenocarcinomas of the pancreas are hypovascular, and neuroendocrine tumors are hypervascular by contrast-enhanced CT, which suggests that contrast-enhanced CT is useful for the differential diagnosis of SCC of the pancreas. However, the diagnosis should be made carefully by contrast enhanced CT for large SCC of the pancreas with necrosis, which may present as a heterogeneously low-density mass on contrast-enhanced CT scanning. In addition, radio-labeled somatostatin analogue scanning is also used to detect metastatic diseases and

Table 3. Multivariate analysis of survival on clinical and pathologic factors.

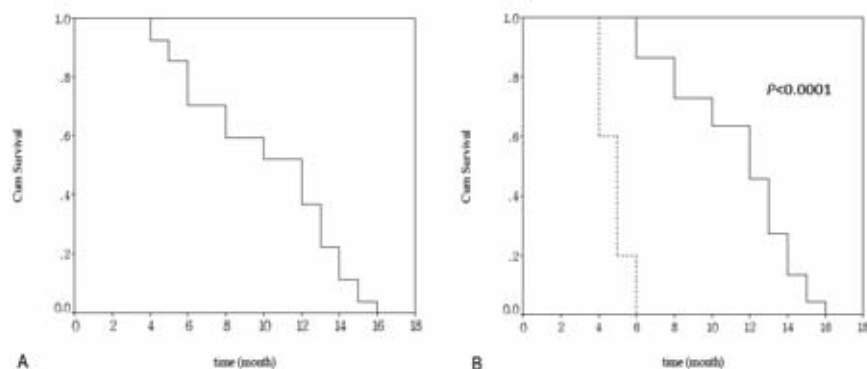| Variables	Hazard ratio (95% CI)	P
Gender	1.44 (0.47-4.46)	0.53
Location	0.96 (0.58-1.59)	0.89
Tumor length (≥4.5 cm)	1.38 (0.18-1.77)	0.56
Pure histology	0.39 (0.03-5.08)	0.39
TNM	2.87 (0.87-9.47)	0.08
Lymph node involvement	0.49 (0.10-2.51)	0.39
Lymphatic vessel invasion	0.56 (0.18-1.77)	0.33
Chemotherapy	0.43 (0.004-0.49)	0.01

CI, confidence interval.

Figure 4. Kaplan-Meier curve of overall survival for the patients. A) Survival curve of patients with small cell carcinoma of the gastrointestinal tract with limited stage; B) survival curves for the patients with and without chemotherapy (Solid line: surgery + chemotherapy; dashed line: surgery; P<0.0001)

evaluate the stage of SCC of the GIT,[26] but its routine use in SCC of the GIT remains controversial.[21]

The diagnosis of SCC of the GIT primarily depends on histopathology, but it is extremely difficult to confirm the diagnosis preoperatively based on the biopsy. In our study, 83.3% cases were diagnosed as undifferentiated adenocarcinoma, squamous carcinoma or other types. The following reasons may account for the misdiagnosis based on the biopsy: first, biopsy specimen is difficult to be obtained because of the proliferations of tumor cells mainly in the submucosal layer; second, histological heterogeneity is common; third, microscopic features usually resemble other malignancies such as malignant lymphoma or undifferentiated carcinoma; and finally, SCC in biopsy material always becomes distorted and obscures the diagnosis.[27,28] Consequently, more tissues and multipoint biopsies should be performed to establish a correct diagnosis. Moreover, electron-microscopical, immunohistochemical and molecular findings are useful for the differential diagnosis. Similar to previous reports,[18,29] our results showed that most of operative specimens were positive for synaptophysin and chromogranin A. However, for the diagnosis of SCC of the GIT, it is unnecessary to make immunohistochemical assessment of neuroendocrine differentiation.[30] Additionally, because of the paucity of SCC of the GIT, it is better to exclude the primary SCC of the lung first when establishing the diagnosis of SCC of the GIT.

SCC of the GIT has a very poor prognosis with a high metastatic potential. The literature reports that the median survival ranges from 6 to 12 months, and the 1-year survival rate varies from 30% to 50% for all stages of SCC of the GIT.[2,6] Not surprisingly, patients with limited stage have a more favorable outcome than those with extensive stage SCC of the GIT. Brenner *et al*. found that the patients of limited stage had a better survival, with a median survival of 21.9 months and a 1-year survival rate of 72% as compared with those with extensive stage, who had a median survival of 5.8 months and a 1-year survival rate of 29% .[2] Lv *et al*. reported a median survival of 14.0 months and a 1-year survival rate of 62.1% for limited stage in a series of esophageal SCC.[10] In our study, the overall median survival and 1-year survival rate were 10 months and 37.0%, respectively. Compared with previous results, the patients in our series had a poorer prognosis due to the small sample size, a higher regional lymph node metastasis (40.7%), and lymphatic invasion (63.0%). In addition, Brenner *et al*. demonstrated that performance status, weight loss and the extent of disease were independent prognostic factors for all stages of SCC of the GIT.[2] Casas *et al*. considered tumor size and additional chemotherapy

as independent prognostic factors in esophageal SCC with limited stage.[31] Chen *et al*. suggested that both surgery and chemotherapy strongly correlated with survival in esophageal SCC with limited stage.[12] Our multivariate analysis found that postoperative chemotherapy significantly improved the outcome of patients with limited stage SCC of the GIT. Unfortunately, similar to other data,[2,10,29] all patients in our group had disease progression or recurrence despite multimodal therapy. Consequently, it is of the utmost importance to perform a study of appropriate regimens for SCC of the GIT with limited stage.

Chemotherapy is now recognized as the cornerstone of treatment for SCC of the GIT because micrometastases are frequently present and the rate of recurrence is high,[10,12,32] even in the setting of limited disease. In our series, postoperative chemotherapy significantly improved survival in patients with limited stage. However, current chemotherapeutic agents for SCC fail to eliminate tumor cells of adeno or squamous phenotype completely.[2,33] Surgery therefore has a potential role in limited stage, given the high prevalence of mixed tumor histology. Yet, the exact role of surgical treatment remains controversial in limited stage. The most important explanation for this controversy is that the survival superiority found for different treatments may reflect a selection bias of more aggressive therapies for more suitable patients who are in better conditions before treatment. Our study could not respond to the question about the role of the surgery in limited stage, although surgical resection was frequently the first choice in our series. Therefore, without randomized controlled trials of treatment, it will remain difficult to draw conclusions about the most effective treatment. In practice, limited stage SCC of the GIT should be regarded as a systemic disease and treated by multimodal approaches.

Conclusions

In conclusion, SCC of the GIT is a relatively rare and aggressive tumor with a dismal prognosis. Our retrospective study shows a survival advantage favoring postoperative chemotherapy for limited stage SCC of the GIT. More prospective studies on a larger scale should be conducted to further illuminate the pathogenesis of limited stage SCC of the GIT and define the optimal therapeutic regimen.

References

1. Duguid JB, Kennedy AM. Oat-cell tumors of mediastinal glands. J Pathol Bacteriol 1930;33:93-9.

2. Brenner B, Shah MA, Gonen M, et al. Small-cell carcinoma of the gastrointestinal tract: a retrospective study of 64 cases. Br J Cancer 2004;90:1720-6.

3. Renner G. Small cell carcinoma of the head and neck: a review. Semin Oncol 2007;34:3-14.

4. Shahab N. Extrapulmonary small cell carcinoma of the bladder. Semin Oncol 2007;34:15-21.

5. Chan JK, Loizzi V, Burger RA, et al. Prognostic factors in neuroendocrine small cell cervical carcinoma: a multivariate analysis. Cancer 2003;97:568-74.

6. Brenner B, Tang LH, Shia J, et al. Small cell carcinomas of the gastrointestinal tract: clinicopathological features and treatment approach. Semin Oncol 2007;34:43-50.

7. Mitani M, Kuwabara Y, Shinoda N, et al. Long-term survivors after the resection of limited esophageal small cell carcinoma. Dis Esophagus 2000;13:259-61.

8. Yachida S, Matsushita K, Usuki H, et al. Long-term survival after resection for small cell carcinoma of the esophagus. Ann Thorac Surg 2001;72:596-7.

9. Takaku H, Oka K, Naoi Y, et al. Primary advanced gastric small cell carcinoma: a case report and review of the literature. Am J Gastroenterol 1999;94:1402-4.

10. Lv J, Liang J, Wang J, et al. Primary small cell carcinoma of the esophagus. J Thorac Oncol 2008;3:1460-5.

11. Ho KJ, Herrera GA, Jones JM, Alexander CB. Small cell carcinoma of the esophagus: evidence for a unified histogenesis. Hum Pathol 1984;15:460-8.

12. Chen SB, Yang JS, Yang WP, et al. Treatment and prognosis of limited disease primary small cell carcinoma of esophagus. Dis Esophagus 2011;24:114-9.

13. Matsui K, Kitagawa M, Miwa A, et al. Small cell carcinoma of the stomach: a clinicopathologic study of 17 cases. Am J Gastroenterol. 1991;86:1167-75.

14. Maitra A, Tascilar M, Hruban RH, et al. Small cell carcinoma of the gallbladder: a clinicopathologic, immunohistochemical, and molecular pathology study of 12 cases. Am J Surg Pathol 2001;25:595-601.

15. Burke AB, Shekitka KM, Sobin LH. Small cell carcinomas of the large intestine. Am J Clin Pathol 1991;95:315-21.

16. Lam KY, Law S, Tung PH, Wong J. Esophageal small cell carcinomas: clinico-pathologic parameters, p53 overexpression, proliferation marker, and their impact on pathogenesis. Arch Pathol Lab Med 2000;124:228-33.

17. Takubo K, Nakamura K, Sawabe M, et al. Primary undifferentiated small cell carcinoma of the esophagus. Hum Pathol

1999;30:216-21.

18. Parwani AV, Geradts J, Caspers E, et al. Immunohistochemical and genetic analysis of non-small cell and small cell gallbladder carcinoma and their precursor lesions. Mod Pathol 2003;16:299-308.

19. Watson KJ, Shulkes A, Smallwood RA, et al. Watery diarrhea-hypokalemia-achlorhydria syndrome and carcinoma of the esophagus. Gastroenterology 1985;88:798-803.

20. Nishimaki T, Suzuki T, Fukuda T, et al. Primary small cell carcinoma of the esophagus with ectopic gastrin production. Report of a case and review of the literature. Dig Dis Sci 1993;38:767-71.

21. O'Byrne KJ, Cherukuri AK, Khan MI, et al. Extrapulmonary small cell gastric carcinoma. A case report and review of the literature. Acta Oncol 1997;36:78-80.

22. Corrin B, Gilby ED, Jones NF, Patrick J. Oat cell carcinoma of the pancreas with ectopic ACTH secretion. Cancer 1973;31:1523-7.

23. Doherty MA, McIntyre M, Arnott SJ. Oat cell carcinoma of esophagus: a report of six British patients with a review of the literature. Int J Radiat Oncol Biol Phys 1984;10:147-52.

24. Ichikawa T, Federle MP, Ohba S, et al. Atypical exocrine and endocrine pancreatic tumors (anaplastic, small cell, and giant cell types): CT and pathologic features in 14 patients. Abdom Imag 2000;25:409-19.

25. Namieno T, Koito K, Nagakawa T, et al. Diagnostic features on images in primary small cell carcinoma of the pancreas. Am J Gastroenterol 1997;92:319-22.

26. Berkel S, Hummel F, Gaa J, et al. Poorly differentiated small cell carcinoma of the pancreas. A case report and review of the literature. Pancreatology 2004;4:521-6.

27. Kusayanagi S, Konishi K, Miyasaka N, et al. Primary small cell carcinoma of the stomach. J Gastroenterol Hepatol 2003; 18:743-7.

28. Brenner B, Tang LH, Klimstra DS, Kelsen DP. Small-cell carcinomas of the gastrointestinal tract: a review. J Clin Oncol. 2004;22:2730-9.

29. Vos B, Rozema T, Miller RC, et al. Small cell carcinoma of the esophagus: a multicentre Rare Cancer Network study. Dis Esophagus 2011;24:258-64.

30. Gaffey MJ, Mills SE, Lack EE. Neuroendocrine carcinoma of the colon and rectum. A clinicopathologic, ultrastructural, and immunohistochemical study of 24 cases. Am J Surg Pathol 1990;14:1010-23.

31. Casas F, Ferrer F, Farrús B, et al. Primary small cell carcinoma of the esophagus: a review of the literature with emphasis on therapy and prognosis. Cancer 1997;80:1366-72.

32. Ku GY, Minsky BD, Rusch VW, Bains M, Kelsen DP, Ilson DH. Small-cell carcinoma of the esophagus and gastroesophageal junction: review of the Memorial Sloan-Kettering experience. Ann Oncol 2008;19: 533-7.

33. Medgyesy CD, Wolff RA, Putnam JB Jr, Ajani JA. Small cell carcinoma of the esophagus: the University of Texas M. D. Anderson Cancer Center experience and literature review. Cancer. 2000;88:262-7.