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ORIGINAL ARTICLE

Management of Small Cell Carcinoma of Esophagus in China

Xu-jing Lu · Ju-dong Luo · Yang Ling · Ying-Ze Kong · Li-Li Feng · Jian Zhou · Feng Wang

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Abstract
Purpose Small cell carcinoma of esophagus (SCEC) is characterized by high malignancy and early metastasis. Although the morbidity of SCEC is very low, few studies of patients with SCEC have been conducted in China, there are no sufficient studies of SCEC conducted and reported in the existing published works, and the choices of treatment remain controversial. In this work, we aim to study the clinical characteristics of SCEC, and explore the corresponding treatment and prognosis through retrospective analysis.
Material and Methods The original articles were identified through the leading digital libraries in China in which the terms "esophagus or esophageal" and "small cell esophageal carcinoma" appeared from 2005 to 2009, 1,176 eligible cases were reviewed for clinical data. Analysis of survival was conducted using the Kaplan–Meier method, and differences were compared using the log-rank test.
Results One thousand one hundred seventy-six eligible cases were analyzed; the median age of patients was 57 years, with a male-to-female ratio of 2.4:1. The number of SCEC accounted for 1.26 % of esophageal cancer treated in the same period. Of the tumors, 89.7 % were located in mid- and lower thoracic esophagus. The average tumor length was 5.4 cm (0.5–17 cm). The median overall survival was 11.1 months for all patients. The 1-, 2-, 3-, and 5-year average overall survival rates of 469 patients was 51.1, 25.5, 13.2, 7.9 %, respectively. The median survival time for LD patients who received systemic treatment was 16.8 m, whereas for those who received local treatment (surgery), the median survival time was 10.1 m; the median survival time for ED patients who received systemic treatment was 7.4 m, compared with 5.8 m for those who received sole treatment (chemotherapy or radiotherapy).
Conclusions SCEC is a tumor characterized by high malignancy and early metastasis. Although our retrospective analysis cannot provide definitive conclusions on the optimal treatment modality for SCEC, however, our results suggest that systemic treatment combined with surgical resection plays a major role in the therapy of SCEC, systemic therapy may be an effective approach for the treatment of SCEC, and randomized, prospective, multicenter studies are needed to identify optimal treatment modalities for SCEC

Keywords Small cell carcinoma · Esophagus · Surgery · Chemotherapy · Radiotherapy · Prognosis

Introduction

Primary small cell carcinoma of the esophagus (SCEC) is a rare disease, which was first described in 1952 by McKeown.[1] In a study on more than 9,000 autopsy specimens, McKeown described two cases of esophageal tumors in post mortem examinations that were morphologically indistinguishable from the well-known primary small cell carcinoma of lung. SCEC is characterized by high malignancy, distant metastasis, and poor prognosis. SCEC is rarely seen with an incidence rate of 0.5–2.4 % among all primary esophageal malignancies in a given period.[2] Only less than 300 cases have been reported in the literature.[3] Treatment protocols have not been well established because of the paucity of cases and a lack of large studies. In recent years, the incidence of primary SCEC in China has been increasing gradually with the development of pathologically

X.-j. Lu (✉) · J.-d. Luo · Y. Ling · Y.-Z. Kong · L.-L. Feng · J. Zhou · F. Wang
Department of Radiation Oncology, Changzhou Tumor Hospital Soochow University, Changzhou 213002, Jiangsu Province, China
e-mail: luxujing68@yahoo.com.cn

diagnostic techniques. In this report, we retrospectively analyzed the clinical manifestations, pathological features, treatment, and prognosis of SCEC.

Materials and Methods

We identified and collected the articles from CNKI and Wanfang Databases that are two of the primary digital libraries providing most comprehensive access to full-text documents of publications in China. The original articles were identified with the keywords and topics related to *esophagus or esophageal* and *small cell carcinoma*, and were published during the period from 2005 to 2009. For a few cases that were reported more than once, we selected the data of these cases from their most recent publications for analysis. All eligible cases were extracted according to a set of recorded features including age, gender, tumor site, histology (pure or mixed), tumor stage (tumor–node–metastasis (TNM) stage or Veterans' Administration Lung Study Group (VALSG) stage), treatment, and follow-up. Local treatment consisted of radiotherapy and/or surgery, and systemic treatment consisted of chemotherapy, radiotherapy, and/or surgery.

The histological criteria for pulmonary small cell carcinoma prepared by the World Health Organization (WHO, sixth edition) were used, and both sole small cell and mixed cell types were considered. 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 (chromogranin A), CK (cytoeratin), CD56 (lymphocyte antigen 56), and others.

Currently, no specific staging system for SCEC has been established. Disease stages were presented according to two staging systems—the 1997 or 2002 American Joint Committee on Cancer (AJCC) TNM staging system for esophageal cancer,[4] and the VALSG staging system for primary pulmonary small cell carcinoma (SCC).[5] The latter one consists of two staging categories including limited disease (LD) and extensive disease (ED). LD is defined as tumor confined within a localized anatomic region with or without regional lymph node involvement. ED is defined as tumor outside locoregional boundaries.[6] The choice of employing different system may depend on the management algorithms adopted. 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. Categorical variables were compared using Fisher's exact or the chi-squared test when appropriate. Overall survival was calculated as the time from diagnosis to death or the last follow-up appointment for surviving patients. Analysis of survival was conducted using the Kaplan–Meier method, and differences were compared using the log-rank test. Statistical significance was defined as a p value that was smaller than 0.05.

Results

A total of 72 original articles on SCEC were published in China during the selected period in our study. Among these articles, there were only 30 eligible articles in which the studies covered 15 provinces and regions of China,[7–36] and the median time of patients collection was 15 years (range from 5 to 40 years).

One thousand one hundred seventy-six patients with SCEC were admitted from these selected 30 articles. The rate of the patients with esophageal in different provinces and regions during the time period ranged from 0.36 to 2.8 %, and the median rate was 1.26 %. Among the 1,176 patients, 830 were males and 346 were females. The male-to-female ratio ranged from 0.44:1 to 5.6:1 across different provinces and regions of the country, and the median ratio was 2.40:1. Moreover, the age ranged from 25 to 87 years, and the median value was 57 years.

Clinical Presentations

We noted that the clinical presentations were dominated by the advanced stage at the time of diagnosis. Clinical symptoms of SCEC were similar to that of squamous carcinoma of the esophagus, and no significant specificity was seen in X-rays imaging and esophagoscopy.[7] we observed that the most common initial symptoms, such as progressive dysphagia and anorexia, were shown in almost all patients (ranging from 78.8 to100%). The other symptoms, including retrosternal pain and swallowing pain, were shown in some advanced patients, and the rates were 22.8 and 15.6 %, respectively. A few patients may have hoarse voice and weight loss, etc. The duration of symptoms before diagnosis varied from 10 days to 20 months, with a mean time of 1 month.

Tumor Characteristics

Tumor characteristics were summarized in Table 1. In particular, the tumor location varied among the patients. For most patients (62.2 %, 731/1,176), the tumors were located in middle of the thoracic esophagus. The tumors were found in the upper third of the thoracic esophagus for 116 patients (9.9 %, 116/1,176), and in lower third of the thoracic esophagus for 324 patients (27.6 %, 324/1,176). Only for five patients (0.4 %), the tumors were found in cervical segment of the esophagus. The tumor length was measured for most patients (77.6 %, 912/1,176). The length ranged from 0.5 to 17 cm, and the average value was 5.4 cm.

Table 1 Tumor clinical characteristics

Characteristics	Patients	
	Number	Percentage, %
Tumor location (n=1,176)		
Cervical	5	0.4 %
Upper thoracic	116	9.9 %
Middle thoracic	731	62.2 %
Lower thoracic	324	27.6 %
Tumor length (cm) (n=912)		
Average	5.4	
Range	0.5–17	
Histological component (n=735)		
Pure SCEC	597	81.2 %
Mixed SCEC	138	18.8 %
Mixed with squamous cell carcinoma	123	
Mixed with adencarcinoma	12	
Mixed with adenosquamous carcinoma	3	
Immunological marker (n=309)		
NSE	268	87.7 % (268/309)
Syn	169	75.8 % (169/223)
CgA	205	71.9 % (205/285)
CK	31	40.3 % (31/77)
CD56	39	97.9 % (39/42)
TNM staging (n=523)		
I	34	6.5 %
IIa	99	18.9 %
IIb	90	17.2 %
III	201	38.4 %
IV	99	18.9 %
VALSG stage (n=467)		
LD	347	74.3 %
ED	120	25.7 %

NSE neuron-specific enolase, *Syn* synaptophysin, *CgA* chromogranin A, *CK* cytoeratin, *CD56* lymphocyte antigen 56, *LD* limited disease, *ED* extensive disease

Only a small part of the patients (27.4 %, 322/1,176) were pathologically confirmed to be esophageal cancer by esophagoscopy and biopsy before operation. Only 74 patients (6.3 %, 74/1,176) were histologically diagnosed with SCEC by esophagoscopy and biopsy before operations. Among the rest of the patients, 62 were pathologically diagnosed to have poorly differentiated squamous cell carcinoma, 24 with poorly differentiated cell carcinoma, and 162 with esophageal squamous cell carcinoma.

Pathological Features

All the patients were diagnosed with SCEC by postoperative histopathology and a part of patients were applied with immunohistochemical staining. The specimens were classified as pure SCEC in 597 cases (81.2 %, 597/735) and mixed esophageal cancer in 138 cases (18.8 %, 138/735). Among the 138 cases, there were 123 cases with squamous cell carcinoma predominance, 12 cases with adencarcinoma, and 3 cases with adeno-squamous carcinoma.

Immunohistochemical study information was available for 309 patients. Staining for five immunological markers (NSE, Syn, CgA, CK, and CD56) was performed on a part of the cases. Specifically, 87.7 % (268/309) of the immunological reactivity of the samples were NSE, 75.8 % (169/223) were Syn, 71.9 % (205/285) were CgA, 40.3 % (31/77) were CK, and 97.9 % (39/42) were CD56.

Stagings

According to the 1997 or 2002 AJCC TNM staging system, of 523 cases studied, there were 34 cases in stage I (6.5 %, 34/523), 99 cases in stage IIa (18.9 %), 90 cases in stage IIIb (17.2 %), 201 cases in stage III (38.4 %), and 99 cases in stage IV (18.9 %). By VALSG criteria, of 467 patients studied, 74.3 % (347/467) of the patients had LD, and 25.7 % (120/467) of the patients presented with ED.

Treatment

Since nearly all patients with SCEC were diagnosed as esophageal squamous cell carcinoma or poorly differentiated carcinoma initially, most patients underwent initial surgical resection.

Of the 1,176 patients studied, 936 patients received surgical resection, in which 885 patients underwent radical resection and 51 patients with palliative operation. The resection rate and radical resection rate were 79.6 % (936/1,176) and 94.6 % (885/936), respectively. Surgery was the sole treatment modality in 277 cases where 263 cases with radical and 14 cases with palliative resection. Adjuvant chemoradiotherapy was used in 565 cases where 391 cases with four to six courses of platinum-based combination chemotherapy, 50 cases with radiotherapy, and 124 cases with chemoradiotherapy, respectively. Other 94 patients did not have the records of adjuvant chemoradiotherapy after surgery,[17, 18] and the comprehensive treatment rate was 60.4 % (565/936).

Two hundred eight patients received nonoperative treatment due to advanced disease, in which 55 patients with chemotherapy, 44 patients with radiotherapy, and 109 patients with chemoradiotherapy, respectively. Five patients did not receive any treatment, and another 27patients did not have any records of treatment information in the articles.[19]

Prognosis

Of the 1,127 patients studied, the median survival time of 403 patients was 11.1 months (range, 10–15 months).[7, 8, 12, 13, 15, 23, 24, 33] The median survival time of patients with and

without lymph node metastasis were 8.5 months (range, 7–10 months) and 14 months (range,13–15 months), respectively.[8, 15] The median survival time for the LD patients who received systemic treatment was 16.8 months (range, 11–38 months), compared with 10.1 months (range, 7.5–12 months) for those who received local treatment (surgery). The median survival time for the ED patients who received systemic treatment was 7.4 months (range, 7.2–8.5 months), compared with 5.8 months (range, 4–7.5 months) for those who received sole treatment (chemotherapy or radiotherapy).[7, 9–13, 15, 16, 19] Table 2 showed our detailed univariate analysis of median survival for SCEC patients.

The 1-, 2-, 3-, and 5-year average overall survival rates of 469 patients were 51.1 % (range, 41.3–67.2 %), 25.5 % (range, 16.1–38.5 %), 13.2 % (range, 6.4–23.3 %), and 7.9 % (range, 3.5–12 %), respectively.[7, 8, 13–15, 18, 23, 24, 33] The 1-, 2-, and 3-year survival rates for the patients with lymph node metastasis were 31.1 % (range, 26.3–35.9 %), 11.4 % (range, 5.2–17.6 %), and 5.3 % (range, 0–10.6 %), respectively. The 1-, 2-, and 3-year survival rates for patients without lymph node metastasis were 77.3 % (range, 75–79.6 %), 42 % (range, 33.3–50.7 %), and 28.6 % (range, 16.6–40.6 %), respectively.[7, 8] The 1-, 2- and 3-year survival rates for the LD patients were 62.1, 28.3, and 12.5 %, respectively, compared with 39.5, 8.2, and 0 % for the ED patients.[7, 8] The 1-, 2- and 3-year survival rates for the patients who received systemic treatment were 69.8, 38.1, and 22.9 %, respectively, whereas for those who received local treatment (surgery), the 1-, 2-, and 3-year survival rates were 28.9, 1.9, and 0 %, respectively.[8, 14] Table 3 showed our detailed univariate analysis of survival rate for SCEC patients.

Discussion

Since the first description of small cell carcinoma in the lungs (SCLC) reported in 1926 and the first description of extrapulmonary small cell carcinoma (EPSCC) in 1930, small cell carcinoma has been observed in many locations within body, and the sites cited so far include the head and neck, esophagus, stomach, pancreas, gallbladder, uterine cervix, kidney, urinary bladder, and prostate. In a few cases, the primary site remains undetected, which has been identified as small cell carcinoma of unknown origin.[37–39] Nearly half of the cases reported in the literature were located in the esophagus.[39, 40] In contrast to SCLC that comprises about 20 % of all lung cancers, EPSCC is uncommon, with an overall incidence of approximately 0.1 to 0.4 % in nonpulmonary sites.[38] Approximately 1,000 new cases of EPSCC are diagnosed yearly in the USA, which represents 2.5–5 % of SCC cases.[37]

Two cases of SCEC were first reported by McKeown in 1952. Although many consecutive cases have been reported since then, only few large series of cases have been reported in either China or other countries.[41, 42] The incidence of SCEC between all esophageal malignancies is from 0.05 to 2.4 % in western populations, and this rate rises up to 7.6 % in Chinese and Japanese literature.[2, 43, 44] The first largest retrospective analysis has been carried out by Casas et al. (1997), who analyzed 199 evaluable patients found in the literature. They reported a male-to-female ratio of 1.57:1, with 95 % of tumors situated in the mid- and lower esophagus. One third of cases were mixed tumors with squamous carcinoma. In our study, SCEC predominantly occurred in males (2.4:1) at a median age of 57 years, with 89.7 % of tumors located in mid- and lower thoracic esophagus, and only 18.8 % of patients were with mixed tumors with squamous or adencarcinoma, which was at variance with other published literature on SCEC.

The most common symptoms were progressive dysphagia and anorexia for nearly all patients. Retrosternal pain (22.8 %) and swallow pain (15.6 %) were also observed in advanced patients, respectively, which were identical to the rate of esophageal squamous cell carcinoma without significant difference. This is because esophageal squamous cell carcinoma is the most common cancer within esophageal tumors in China.[45]

Our group observed a lower preoperative diagnostic rate of 6.3 %, in which most patients were pathologically confirmed to have squamous cell carcinoma or poorly differentiated cell carcinoma by preoperative esophagoscopy biopsy. The main reason was that a small amount of tissues were picked for endoscopic biopsy which could be limited for the diagnosis of complex small cell carcinoma and sometimes incur difficulties to differentiate SCEC from poorly differentiated squamous cell carcinoma. Of the 322 patients with preoperative esophagoscopy and biopsy, 86 cases were histologically diagnosed with poorly differentiated cell carcinoma or poorly differentiated squamous cell carcinoma. Therefore, more tissues and multipoint biopsy should be obtained under

Table 2 Univariate analysis of median survival for SCEC patients

	Median survival (months, range)
Total	11.1 (10–15)
Lymph node metastasis	
N0	14 (13–15)
N+	8.5 (7–10)
Limited disease	
Local treatment	10.1 (7.5–12)
Systemic treatment	16.8 (11–38)
Extensive disease	
Local treatment	5.8 (4–7.5)
Systemic treatment	7.4 (7.2–8.5)

N0 lymph node negative, *N+* lymph node positive

Table 3 Univariate analysis of survival rate for SCEC patients

	No. of cases	Survival rate (%,range)			
		1 year	2 year	3 year	5 year
Total	469	51.1 (41.3–67.2)	25.5 (16.1–38.5)	13.2 (6.4–23.3)	7.9 (3.5–12)
Lymph node metastasis					
N0	45	31.1 (26.3–35.9)	11.4 (5.2–17.6)	5.3 (0–10.6)	
N+	84	77.3 (75–79.6)	42 (33.3–50.7)	28.6 (16.6–40.6)	
VALSG stage					
LD	176	62.1 (59.4–64.7)	31.2 (28.3–34.1)	12.5 (5.1–19.8)	
ED	17	39.5 (33.3–45.6)	8.2 (0–16.4)	0	
TNM stage					
I	16	80.0	66.7	33.3	
IIa	21	81.3	43.8	43.8	
IIb	23	58.2	25.5	12.7	
III	66	43.8	11.7	8.8	
IV	25	47.6	17.9	6.0	
Treatment					
Local treatment	39	28.9 (20–37.9)	1.9 (0–3.8)	0	
Systemic treatment	83	69.8 (50–89.5)	38.1 (21.4–57.6)	22.9 (11.7–40.0)	

N0 lymph node negative, *N+* lymph node positive, *LD* limited disease, *ED* extensive disease

esophagoscopy to carry out a diagnosis in a more accurate fashion.

At present, the pathogenesis of SCEC is controversial and remains speculative.[37, 44] A leading hypothesis is that SCEC may originate from a pluripotent stem cell of the endoderm, which may be partially differentiated into squamous cell carcinoma and partially into adenocarcinoma or small cell carcinoma because of the stimulation of different carcinogenic agent. This is mainly due to the diversity of morphological, immunohistological, and electron microscopic features of SCEC, in addition to the coexistence of SCEC with squamous cell carcinoma and /or adenocariconoma. In the present study, we noted that 18.8 % of SCEC patients were with elements of adenocariconoma or squamous cell carcinoma, and this observation supported this hypothesis in a positive fashion.

Limited data are available in the literature describing the optimal management of patients with SCEC due to its lower incidence rate and limited knowledge to the disease,[37, 38, 44] and there are no randomized controlled trials of treatment and it is difficult to draw conclusions about effective treatment from clinical series alone. In a multivariate analysis performed, Casas et al. reported that in SCEC patients, the median survival of patients who were treated with local therapy only was 5 months. In patients who received local treatment plus chemotherapy, the median survival was 20 months. They concluded that the addition of chemotherapy to local treatment should be considered as standard treatment for limited disease of SCEC.[2] A recent retrospective study by Ding et al. reported different treatments of limited-stage SCEC patients; combined modality treatment with and without chemotherapy yield 5-year survival rates of 27.2 and 0 %, respectively, and associated median survival times were 22 and 11 months, respectively (p=0.001).[46] But there was still some debate about whether surgery or radiotherapy optimizes local treatment.[3] Our data indicated that the median survival time of LD patients who received systemic treatment was 16.8 months, and 3-year survival rate was 12.7 %, whereas that of LD patients who received local treatment was only 10.1 months, and none could survive for more than 3 years. The median survival of ED patients who received systemic treatment was 7.4 months, whereas that of ED patients who received local treatment was only 5.8 months. For either limited stage or extensive stage, systemic treatment combined with surgical resection appeared to be a good option. In the therapy of SCEC, randomized, prospective, multicenter studies are needed to identify optimal treatment modalities for SCEC.

Small cell lung cancer (SCLC) patients whose cancer can be controlled outside the brain have a 60 % risk of developing central nervous system metastases within 2 to 3 years after primary treatment,[47, 48] and can be considered for administration of prophylactic cranial irradiation (PCI), the risk of developing central nervous system metastases can be reduced by more than 50 % by the administration of PCI in doses of 24 Gy.[48, 49] But brain metastases in SCEC patients were rarer than in SCLC.[3, 38, 50–54] Our data indicated that brain metastases were uncommon in SCEC, and were

observed in only 2 of 185 patients.[7, 15] Because the difference in incidence of brain metastasis at presentation and during follow-up between SCEC and SCLC, efficacy Of PCI for SCEC are lacking, we do not recommend a routine usage for SCEC patients.

Conclusions

In summary, SCEC is a tumor characterized by high malignancy and early metastasis; because of the lower incidence rate of SCEC, it is hard to conduct a randomized controlled trial so as to find a new therapeutic strategy. Despite rare reports of long-term survivors of SCEC compared with other esophageal cancer types, some patients were cured. Although our retrospective analysis cannot provide definitive conclusions on the optimal treatment modality for SCEC, however, our results suggest that systemic treatment combined with surgical resection plays a major role in the therapy of SCEC, systemic therapy may be an effective approach for the treatment of SCEC, and randomized, prospective, multicenter studies are needed to identify optimal treatment modalities for SCEC.

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