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Research Article

Small Cell Carcinoma of the Esophagus in China: A Systematic Review and Meta-Analysis

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Abstract

Objective: To survey and analyze the incidence and effect of treatment of small cell carcinoma of the esophagus in China over the past decade and to explore the future of esophageal small cell carcinoma-related problems.

Methods: We undertook a systematic review and meta-analysis of the small cell carcinoma of the esophagus incidence, evaluation of the effectiveness of various treatments and effects of cancer staging on survival. Search strategies were conducted in the China Digital Library CNKI database were identified by searching for the terms “esophagus” and “Small cell carcinoma of the esophagus”. A total of 51 articles that appeared between January 2000 and December 2012 were retrieved. A total of 1456 eligible cases were reviewed, and data from the most recent publications.

Results: A total of 1456 cases were reviewed, with patients having a median age of 57.39±3.697 years and with a male to female ratio of 2.4:1. SCEC accounted for 1.14% of esophageal cancer during this period. The average length of the tumors was 5.24±0.83 cm. The median overall survival for all patients was 13.42±4.05 months. The average overall one-, two-, three- and five-year survival rates for the 1153 patients were 52.05%, 25.21%, 18.62% and 7.27%, respectively. Surgery combined with adjuvant chemotherapy in patients resulted in the longest median survival time of 14.94±5.15 months; however, the five-year survival rate between the various treatments showed no difference ($P > 0.05$). TNM staging affected the five-year survival rate ($P < 0.05$) and median survival times of 15.62±3.40 and 15.49±3.96 months were recorded for stage I and IIa patients, respectively.

Conclusion: The total incidence rate of esophageal small cell carcinoma did not increase significantly. Surgery combined with chemotherapy helped to extend the median survival time and early treatment was shown to improve the five-year survival rate. Our work shows that a prospective, multicenter study is the way of the future and is needed to discover new methods of diagnosis, early diagnosis and early treatment and to identify optimal treatment modalities for SCEC.

Keywords: Chemotherapy;Esophagus;Prognosis; Radiotherapy;SmallCell Carcinoma;Surgery

Introduction

China has a high incidence of esophageal cancer, with the 2008 global cancer statistics showing that the incidence of esophageal cancer in China was the 4th highest in the world [1]. Previously, primary Small Cell Carcinoma of the esophagus (SCEC) was considered to be a rare disease. By 1999, China had reported 174 cases [2], with an incidence rate of 0.7-5.1% among all primary esophageal malignancies in a given period. However, since the year 2000, the incidence of SCEC in China has been increasing gradually with the development of pathological diagnosis techniques. In this study, we retrospectively analyzed the clinical manifestations, treatments and prognosis of SCEC to make inferences about the future development of small cell carcinoma of the esophagus.

Materials and Methods

Articles were identified and collected from the China

Digital Library CNKI, which is a database of full-text Chinese publications. The original articles, appearing between January 2000 and December 2012, were identified using the terms "esophagus" and "Small cell carcinoma of the esophagus". We selected all eligible patients from these documents and recorded parameters such as age, gender, tumor site, histology (pure or mixed), tumor stage (TNM stage), treatment and follow-up. Treatments included surgery, preoperative neoadjuvant chemotherapy, postoperative chemotherapy, postoperative radiotherapy and postoperative adjuvant radiotherapy + chemotherapy. 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. Disease stages were presented according to the 2002 American Joint Committee on Cancer (AJCC) TNM staging system for esophageal cancer[3].

Statistical Analyses

We computed the mean standard deviation of the continuous variables and the differences were compared using the Kruskal–Wallis test. A comparison of the survival curves was conducted using the Kaplan–Meier method and differences were compared using the log-rank test. The Cox proportional hazards model with stepwise regression was used for multivariate analysis. Statistical significance was defined as a p value of less than 0.05.

Results

A total of 51 articles (1456 reported cases) on SCEC were published during the selected period in China [4-52], of which 19 articles reported 55,167 cases of esophageal cancer [4,5,10,21,23-25,28,30,31,35,41,42,48,49,50-53]. SCEC accounted for 1.14% of esophageal cancer during this period (630/55167).

The reported cases ranged throughout the 17 Chinese provinces (Figure 1) and were distributed in Middle-Eastern China. Traditionally, a high incidence of esophageal cancer has been found in the following areas: China Taihang Mountains, the Qinling ministry area, the Dabie Mountain area, northern Sichuan, Fujian, the Guangdong Chaozhou-Shantou area and northern Jiangsu[53]. All reported cases of esophageal small cell carcinoma were found in these areas. The gender statistics (n=1405) included 1017 males and 388 females, with a male to female ratio of 2.4:1. The age of the cases ranged from 26 to 85 years, with the average age being 57.39±3.697 years.

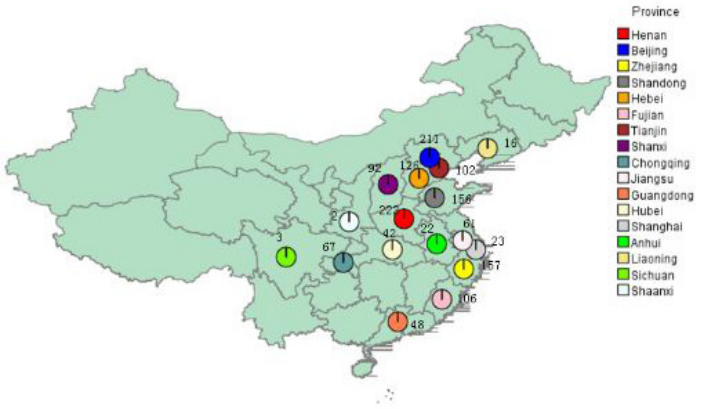

Figure 1: Regional distribution of small cell carcinoma of esophagus in China.

Previous studies showed clinical symptoms similar to squamous cell carcinoma, with the most common first symptoms being progressive dysphagia and anorexia. Other symptoms included chest pain and pain on swallowing and a small number of patients could have a hoarse voice and weight loss.

The tumor characteristics are summarized in Table 1. In three cases (0.22%), the tumors were found in the cervical segment of the esophagus. The tumors were located in the upper third of the thoracic esophagus in 136 cases (10.04%), in the mid-esophagus in 796 cases (58.79%) and in the lower thoracic segment in 419 cases (30.95%). The exact size of the tumor was measured in 1354 cases, with the average length being 5.24±0.83 cm. All patients (n=1456) were pathologically diagnosed with small cell carcinoma of the esophagus, and the specimens were classified as sole SCEC in 1,317 cases (90.45%, 1317/1456) and mixed carcinoma of the esophagus in 119 cases (8.17%, 119/1456). Of the 119 cases, there were 81 with squamous cell carcinoma predominance, 22 with adenocarcinoma and 16 with Adenosquamous carcinoma. 293 patients (20.12%) underwent preoperative endoscopy biopsy to confirm the diagnosis.

Characteristics	Patients	
	Number	Percentage, %
Totle		
esophageal carcinoma	55167	
esophageal small cell carcinoma	1456	
rate	630/55167	1.14%
Sex (n=1405)		
male	1017	72.38%
female	388	27.62%
Male/female ratio	2.6:1	
Age. yr		
average	57.39±3.697	
range	26~85	
Tumor location (n=1354)		
cervical	3	0.22%
upper thoracic	136	10.04%
middle thoracic	796	58.79%
lower thoracic	419	30.95%
Tumor length (cm)		
average	5.24±0.83	
Histological type (n=1456)		
sole	1317	90.45%
mixed	119	8.17%
with squamous cell carcinoma	81	5.56%
with adenocarcinoma	22	1.51%
with adenosquamous carcinoma	16	1.10%
TNM staging (n=824)		
I	62	7.52%
IIa	227	27.55%
IIb	107	12.99%
III	313	37.99%
IV	115	13.96%
Data are presented as mean±SE or No.(%)		

Table1: Characteristics of Study Patients.

According to the 2002 AJCC TNM staging system, of the 824-TNM staged patients, 62 were in stage I (7.52%, 62/824), 227 were in stage IIa (27.55%), 107 were in stage IIb (12.99%), 313 were in stage III (37.99%) and 115 were in stage IV (13.96%).

Of the 1,153 patients studied, 961 received surgical resection, including 147 with a sole operation, 36 received preoperative neoadjuvant chemotherapy, 100 were treated with postoperative adjuvant radiotherapy, 511 were treated with adjuvant chemotherapy and 167 were treated with postoperative chemotherapy combined with radiotherapy.

In the 1,153 patients studied, the median survival time was 13.42±4.05 months. The median survival time for the preoperative neoadjuvant chemotherapy patients was 12.85±3.10 months, for the sole surgery patients was 13.38±4.64 months, for the postoperative adjuvant-chemotherapy patients was 14.94±5.15 months and for the postoperative adjuvant radiotherapy with chemotherapy patients was 12.49±3.08 months. Table 2 shows a detailed univariate analysis of the median survival rate in SCEC patients.

Treatment	Cases	Survival rate (%)				Median survival time (months)
		1 year	2 years	3 years	5 years	
Totle	1153	52.05%	25.21%	18.62%	7.27%	13.42±4.05
Preoperative chemotherapy	36	56.20%	28.62%	17.40%	9.07%	12.85±3.10
Surgery	961	53.23%	26.69%	18.79%	7.50%	13.38±4.64
Postoperative radiotherapy	100	39.43%	26.48%	16.56%	6.17%	14.19±2.82
Postoperative adjuvant chemotherapy	511	52.60%	28.55%	18.94%	6.78%	14.94±5.15
Postoperative adjuvant radiotherapy and chemotherapy	167	51.17%	27.62%	13.85%	7.91%	12.49±3.08
Data are presented as mean±SE or No.(%) unless otherwise indicated.						

Table 2: UnivariateAnalyses for the Treatment of Patients with Primary Esophageal Small CellCarcinoma.

The average overall one-, two-, three- and five-year survival rates for the 1153 patients were 52.05%, 25.21%, 18.62% and 7.27%, respectively, for the 36 patients who received preoperative chemotherapy were 56.20%, 28.62%, 17.40% and 9.07%, respectively, for the 147 patients who received sole surgery were 53.23%, 26.69%, 18.79% and 7.5%, respectively, for the 100 patients who received postoperative radiotherapy were 39.43%, 26.48%, 16.56% and 6.17%, respectively, for the 511 patients who received postoperative adjuvant chemotherapy were 52.60%, 28.55%, 18.94% and 6.78%, respectively and for the 167 patients who received postoperative adjuvant radiotherapy with chemotherapy were 51.17%, 27.62%, 13.85% and 7.91%, respectively. However, there were no statistically significant differences between the different treatment methods ($p>0.05$) (Figure 2,3).

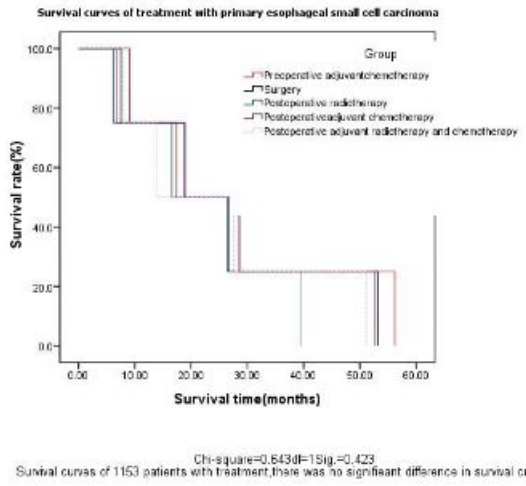

Figure 2: Survival Curves of Treatment with Primary Esophageal Small Cell Carcinoma.

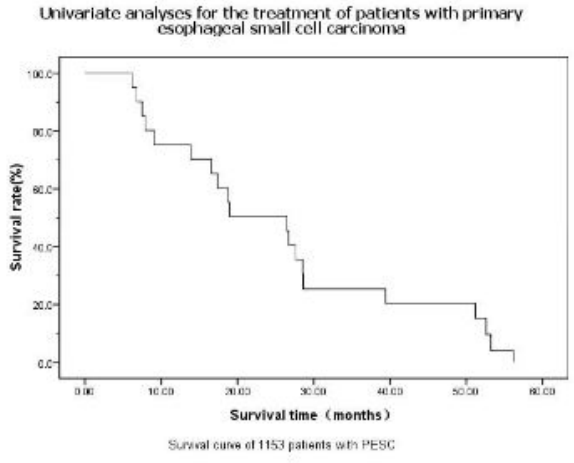

Figure 3: Univariate Analyses for the Treatment of Patients with Primary Esophageal Small Cell Carcinoma.

The survival rate of patients with different stages of SCEC by univariate analysis (Table 3) showed that the SCEC tumor stage was related to the patient survival rate. Stage I patients had a median survival rate of 15.62±3.40 months. The one-, two-, three- and five-year survival rates for the 62 stage I patients were 87.57%, 65.08%, 41.53% and 7.39%, respectively, for the 227 stage IIa patients were 59.21%, 41.95%, 39.34% and 6.0%, respectively, for the 107 stage IIb patients were 59.98%, 28.35%, 15.04% and 0, respectively, for the 313 stage III patients were 39.1%, 14.46%, 12.57% and 0, respectively, and for the 115 stage IV patients were 38.62%, 19.35%, 14.11% and 0, respectively. There were significant differences between the survival rates of patients at the different stages ($p<0.05$) (Figure 4,5).

TNM stage	cases	Survival rate(%)				Median survival time (months)
Totle	824	1 year	2years	3years	5years	
I	62	87.57	65.1	41.5	7.39	15.62±3.40
IIa	227	59.21	42	39.3	6	15.49±3.96
IIb	107	59.98	28.4	15	0	10.23±0.99
III	313	39.1	14.5	12.6	0	9.35±0.98
IV	115	38.62	19.4	14.1	0	7.51±3.99
Data are presented as mean±SE or No.(%) unless otherwise indicated.						

Table 3: Univariate analyses for the TNM stage of patients with primary esophageal small cell carcinoma.

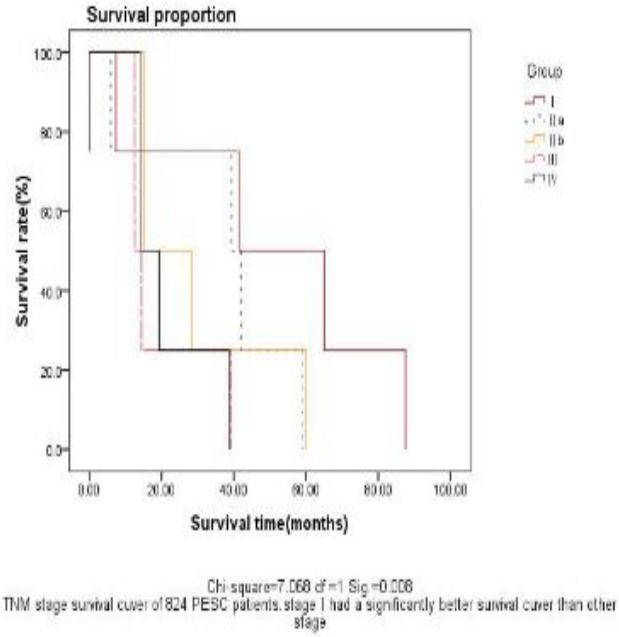

Figure 4:TNM Stage Survival Curve of 824 PESC Patients.

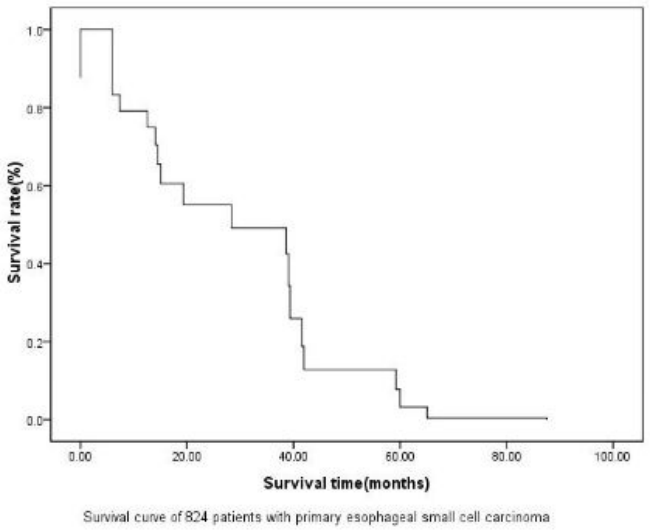

Figure 5: Survival Curve of 824 Patients with Primary Esophageal Small Cell Carcinoma.

Discussion

Over the past decade, the number of reported cases of esophageal small cell carcinoma has increased in China, but the overall incidence rate has remained stable. The incidence of esophageal small cell carcinoma within all esophageal malignancies was 1.14%. American authors have reported an incidence of 0.05 to 2.4%[54]. In this report, the regions in which cases of small cell carcinoma of the esophagus were reported were consistent with the areas of China in which a high incidence of esophageal cancer have been traditionally reported. Viewed from the geographical distribution of cases, these regions have had the fastest growing economy over the past 30 years. SCECs and the incidence of esophageal squamous carcinoma were positively correlated. In the past few decades, the incidence of esophageal squamous cell carcinomas in western countries has been stable or declining [55], while the incidence of esophageal adenocarcinoma has been rapidly increasing. According to the Zeng[56]prediction of trends in incidence of esophageal cancer in China, from 1998 to 2007, the incidence of esophageal squamous cell carcinoma was declining overall. In the cities, the annual standardized incidence rate decreased to 2.1% in men and 7.5% in women. This shows that the basic trend of the incidence of esophageal squamous cell carcinoma in China was in line with that in Western countries, but that there was a lack of a large-scale epidemiological survey of esophageal small cell carcinoma in China. It is not yet certain whether the increase in literature reported cases represents the true incidence of the disease and it is difficult to use statistical results to truly reflect the overall incidence.

For small cell carcinoma of the esophagus, our current understanding is that SCEC is characterized by high malignancy, distant metastasis and poor prognosis. For small cell carcinoma of the esophagus, X-ray imaging and endoscopy clinical symptoms are similar to those observed in esophageal squamous carcinoma and adenocarcinoma. Hence, it is necessary to rely on histological diagnosis, as the preoperative diagnosis rate is not high. In our group, the preoperative diagnostic rate of the patients was 20.12%, which is higher than other literature reports where most patients were pathologically confirmed to have squamous cell carcinoma or poorly differentiated cell carcinoma by preoperative esophagoscopy biopsy. The main reason for this difference is that a small amount of tissue was selected for the endoscopic biopsy, which could limit the diagnosis of complex small cell carcinomas and make it difficult to differentiate between SCEC and poorly differentiated squamous cell carcinoma. Because the pathological diagnosis of some patients before surgery is not accurate, the effect of the combined treatment is not ideal. Hence, improving the preoperative diagnostic rate is a problem to be solved in the future.

The risk factors of esophageal small cell carcinoma are unclear, and whether smoking, alcohol consumption and environmental and dietary changes increase its incidence needs further study. Mixed small cell carcinoma of the esophagus was present in 8.17% of the patients in this group. For 796 cases (58.79%), the tumors were located in the mid-esophagus and for 419 cases (30.95%), they were located in the lower thoracic segment. In only three cases (0.22%), the tumors were found in the cervical segment of the esophagus, as reported by Casas et al.[54]. A leading hypothesis is that SCEC could originate from a pluripotent stem cell of the endoderm, which could differentiate into squamous cell carcinoma and adenocarcinoma or small cell carcinoma due to the stimulation of different carcinogenic agents[57]. However, the specific cause is not known and also something to figure out in the future. Small cell neuroendocrine carcinoma-derived markers, NSE, Syn and CgA, are expressed at high levels[58]. Results can be combined with endoscopy in pathological diagnosis and immunohistochemistry test results to improve the accuracy of diagnosis.

For small cell carcinoma of the esophagus, the best treatments are still unknown. Currently, the recommended treatment is a plastin-like drug based chemotherapy treatment. Casas'[54] retrospective analysis of 199 cases of small cell carcinoma of the esophagus showed that treatment with chemotherapy resulted in a survival benefit in patients with limited stages and that comprehensive treatment was better than a single treatment. To accept the prognosis of a patients' sole surgery is not ideal, as transfers tend to occur within a short period of time after surgery. This is similar to our study, which showed that postoperative adjuvant chemotherapy prolonged the median survival rate (14.94±5.15 months) more than other treatments. However, the

effects of the different treatments on the five-year survival rate were not statistically significant. Furthermore, surgery combined with chemotherapy for early stage patients is still preferred, while chemotherapy combined with radiotherapy in the treatment of advanced cases is currently a more agreeable treatment option. Currently, there is no prospective, randomized controlled study of the treatment options and guidelines of small cell carcinoma of the esophagus. Walker et al.[59]also believed that surgery was the best means of local control, but the system has been combined with chemotherapy treatment. In China, patients with small cell carcinoma of the esophagus are often already at an advanced stage; therefore, the choice of systemic treatments is necessary. Attar et al.[60]found a 90% incidence of metastases in the liver, 25% in the lungs and 1% in the brain by autopsy of small cell carcinoma of the esophagus. Mandrd et al.[61] studied 23 autopsy cases of small cell carcinoma of the esophagus and found 91% metastasis in the lymph nodes and 87% in the visceral organs. Thus, small cell carcinoma of the esophagus should be considered a systemic disease, and it is necessary to implement systemic chemotherapy to treat it. However, the survival rate of the patients receiving chemotherapy is not high; therefore, in these patients, after chemotherapy is used to achieve systemic control, radiotherapy or surgery should be performed to achieve local control. Our study showed that the tumor stage affected the prognosis of SCEC, with higher rates of the five-year survival in patients with stage I or IIa disease. Therefore, early detection and early treatment is the key to improving overall survival.

Conclusion

The risk factors for esophageal cancer include age, smoking, drinking, esophageal reflux disease, human papillomavirus infection, eating pickled foods, trace elements and vitamin deficiency. As the Chinese diet and lifestyle change, it is expected that the incidence of esophageal small cell carcinoma will increase. However, the direct link between the environment and changes in diet structure and the increase in incidence of SCEC still needs to be further researched. The goal is to reduce the mortality due to small cell carcinoma of the esophagus. Therefore, to cure the disease, it is necessary to improve the environment and food safety and to eliminate possible risk factors in the high incidence areas. Early detection and early treatment are the most effective measures with which to improve the five-year survival rate, so future efforts need to focus on finding new tumor markers and new diagnostics. Currently, targeted drug research and research on the development of small cell carcinoma and small cell carcinoma of the esophagus gene polymorphisms is lacking. To sum up, we need to improve the detection level of small cell carcinoma of the esophagus and the ability of patients to choose feasible individualized treatments and discover new drugs in order to really improve the survival rate of small cell carcinoma of the esophagus patients.

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