



Survival analysis of small cell carcinoma of the esophagus: a 15-year retrospective study from a high-incidence region

Wei Zhang¹, Jie Yuan², Baihua Yang¹, Jiezhong Wang¹, Mingqiu Chen¹

¹Department of Thoracic Radiotherapy, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, China;

²Department of Medical College, Fujian Health College, Fuzhou, China

Contributions: (I) Conception and design: W Zhang, J Yuan; (II) Administrative support: W Zhang; (III) Provision of study materials or patients: J Yuan, M Chen, J Wang; (IV) Collection and assembly of data: W Zhang, J Yuan, B Yang; (V) Data analysis and interpretation: W Zhang, J Yuan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Wei Zhang, MSc. Department of Thoracic Radiotherapy, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, No. 420 Fuma Rd., Fuzhou, 350014, China. Email: zhangwei86fz@fjmu.edu.cn.

Background: Small cell carcinoma of the esophagus (SCCE) is a rare malignant carcinoma, which is highly aggressive and prone to recurrence and metastasis. There is no standard therapeutic modality for SCCE. We aimed to describe the clinical characteristics and therapeutic outcomes of SCCE, analyse its prognostic factors, and provide a reference for establishing a standard treatment regimen.

Methods: We retrospectively evaluated 156 consecutive patients with SCCE, who received treatment at Fujian Cancer Hospital between 2007 and 2022. We finally included 140 patients in the analysis. The primary endpoint was overall survival (OS); the key secondary endpoint was progression-free survival (PFS). Multivariate Cox regression survival analysis was conducted to identify the independent prognostic factors. Subgroup analysis included treatment modalities used to patients with limited stage SCCE (LS-SCCE).

Results: The median OS was 24.0 [95% confidence interval (CI): 19.391–28.609] months and the 1-, 3-, and 5-year OS rates were 79.3%, 20.0%, and 9.3%, respectively. The multivariate Cox analysis suggested that chemotherapy was an independent prognostic factor [hazard ratio (HR) 0.519; 95% CI: 0.271–0.992; $P=0.047$]. In subgroup analysis for patients with LS-SCCE, the median OS was 26 months for patients receiving surgery-based multimodal therapy [surgery (S) ± chemotherapy (CT) ± radiotherapy (RT)] compared to 31 months for those receiving definitive chemoradiotherapy (CRT) ($P=0.97$). There was no significant difference between the two groups.

Conclusions: Our results suggest that CRT might be an effective first-line treatment for LS-SCCE and is not inferior to surgery. The conclusions are expected to provide a reference for the standardised treatment of SCCE.

Keywords: Small cell carcinoma of the esophagus (SCCE); chemotherapy; survival analysis

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Introduction

Small cell carcinoma of the esophagus (SCCE), initially described by McKeown *et al.* in 1952 (1), represents a rare and highly aggressive subtype of esophageal malignancy. Accounting for merely 0.1–2.8% of all esophageal cancers (2–6), SCCE exhibits significantly more aggressive

biological behavior compared to other histological subtypes, including esophageal adenocarcinoma and squamous cell carcinoma.

Characterized by extensive neovascularization and rapid proliferative activity, SCCE frequently presents with metastatic dissemination at diagnosis, contributing to its dismal prognosis (4,7,8). The scarcity of cases and poor

clinical outcomes have hindered the conduct of prospective randomized trials or large-scale retrospective analyses. Consequently, no standardized treatment protocol has been established for SCCE to date. Given its pathological and molecular resemblance to small-cell lung cancer (SCLC), current therapeutic strategies for SCCE often adopt a multimodal approach, incorporating chemotherapy, radiotherapy, and surgical resection (9,10). Despite these interventions, the 5-year overall survival (OS) remains strikingly low, ranging from 6.7% to 18%, and factors affecting the overall outcome are unknown because of the lack of long-term follow-up studies.

To address these knowledge gaps, this study retrospectively analysed the clinicopathological features and survival outcomes of SCCE patients treated at our institution between 2007 and 2022. Our objectives were to identify key prognostic factors and provide preliminary insights to guide treatment strategies for this rare malignancy. We present this article in accordance with the STROBE reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-2025-414/rc>).

Highlight box

Key findings

- Chemoradiotherapy might be an effective first-line treatment for limited stage small cell carcinoma of the esophagus (LS-SCCE) and is not inferior to surgery.

What is known and what is new?

- Small cell carcinoma of the esophagus (SCCE) is a rare but highly aggressive malignancy with a propensity for early metastasis. Due to its rarity, no standardized treatment protocol exists. Consequently, the optimal treatment strategy, particularly for LS-SCCE, remains controversial, with debate persisting between surgery-based multimodal therapy and definitive chemoradiotherapy.
- This large single-institution retrospective study of 140 SCCE patients provides a homogeneous analysis with detailed treatment data. It confirms chemotherapy as an independent prognostic factor for overall survival. Crucially, our subgroup analysis of LS-SCCE patients found no significant difference in overall or progression-free survival between those treated with surgery-based multimodal therapy and those receiving definitive chemoradiotherapy, suggesting chemoradiotherapy is a viable non-inferior first-line option. These findings offer valuable insights for standardizing treatment strategies for this rare cancer.

What is the implication, and what should change now?

- The conclusions are expected to provide a reference for the standardised treatment of SCCE.

Methods

Patient selection

Data from 156 consecutive patients with SCCE treated at the Fujian Cancer Hospital (Clinical Oncology School of Fujian Medical University) between January 1st, 2007 and December 31st, 2022, were retrospectively evaluated. All cases were confirmed by the pathological diagnosis of SCCE, including cases mixed with other pathological types, such as squamous cell carcinoma or adenocarcinoma. SCCE was the dominant type of combined carcinoma in all the cases. Sixteen patients were excluded due to incomplete clinical records, treatment discontinuation, or loss to follow-up, yielding a final cohort of 140 adults (age ≥ 18 years) (Figure 1). At the time of initial diagnosis, all enrolled patients received a standardized diagnostic workup that included complete clinical history documentation, thorough physical examination, comprehensive laboratory testing, and upper gastrointestinal endoscopy with confirmatory histopathological assessment. The staging evaluation further consisted of esophageal barium studies, contrast-enhanced computed tomography scans encompassing the neck, thoracic region and upper abdominal compartment, dedicated brain magnetic resonance imaging (MRI), and either whole-body positron emission tomography-computed tomography (PET-CT) or bone scintigraphy for metastatic survey.

Staging and treatment modalities

Given the absence of a standardized staging system specific to SCCE, we adopted dual staging criteria in this study: the Veterans Administration Lung Study Group (VALSG) classification (11,12), which stratifies disease into limited stage (LS, confined to a localized anatomical region without distant metastasis) and extensive stage (ES); and the 8th edition American Joint Committee on Cancer (AJCC) staging manual for esophageal and esophagogastric junction carcinomas (13).

Treatment strategies were determined by multidisciplinary team discussion based on disease stage, patient performance status, and patient preference. Among the 140 selected patients, 84 patients underwent surgery as a part of their treatment, while 14 patients underwent surgery as the only treatment modality. Among the 56 patients who received non-operative treatment, 40 received chemoradiotherapy (CRT), 12 received chemotherapy alone, and four received radiotherapy alone. Regarding the chemotherapy regimen for SCCE, 122 patients received etoposide combined with cisplatin or carboplatin

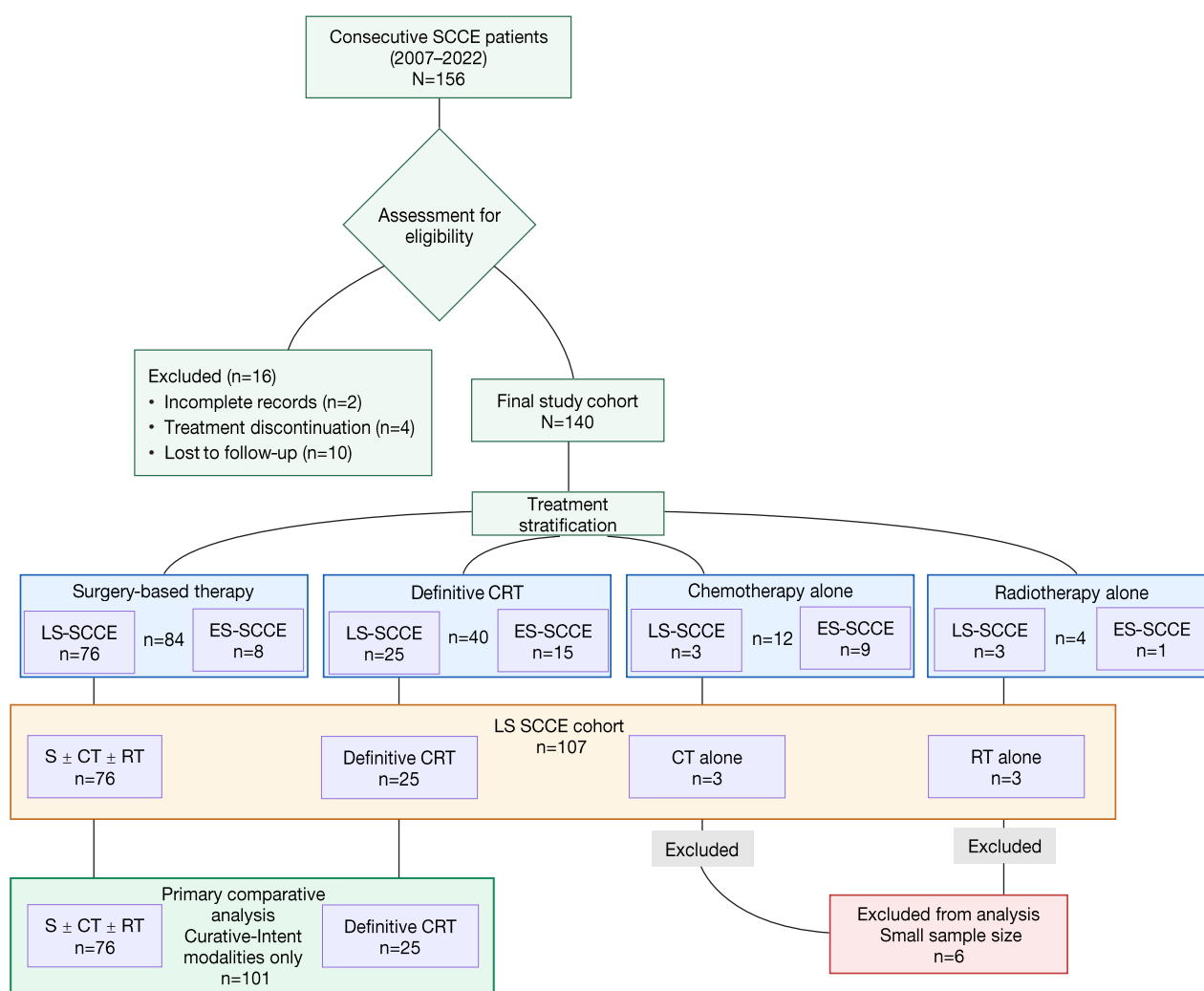


Figure 1 Flowchart of patient selection and treatment group stratification. CRT, chemoradiotherapy; CT, chemotherapy; ES-SCCE, extensive stage-SCCE; LS-SCCE, limited stage-SCCE; RT, radiotherapy; SCCE, small cell carcinoma of the esophagus; S, surgery.

(EP/EC) as the first-line regimen. Fifty-two patients received fewer than four cycles of chemotherapy, four patients received more than six cycles of chemotherapy, and 66 patients received 4–6 cycles of chemotherapy. Radiotherapy was performed using intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) with 1.8–2.0 Gy per fraction. The total radiation dose was 40–64 Gy. Of the 55 patients who received radiotherapy, 10 received postoperative CRT, one received neoadjuvant CRT, 40 received CRT, and four received radiotherapy alone.

Outcome measurements and endpoint

Treatment efficacy was assessed using the Response

Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1) after first-line therapy. The primary endpoint was OS, defined as the time from pathological diagnosis to death from any cause or last follow-up (censored at December 31, 2023). Secondary endpoints included progression-free survival (PFS), defined as the time from pathological diagnosis to disease progression or death from any cause; objective response rate (ORR), comprising complete response (CR) and partial response (PR).

Assessment cause of death and pattern of recurrence

Causes of death were comprehensively reviewed and categorized into three distinct groups: (I) death from disease

progression, defined as mortality directly attributable to tumor advancement; (II) treatment-related mortality, defined as death resulting from complications of anticancer therapy; and (III) non-cancer-related death, defined as mortality from causes unrelated to either the malignancy or its treatment.

Patterns of first disease recurrence or progression were rigorously assessed based on imaging studies and clinical findings. These were classified into the following sites: (I) local recurrence/progression at the primary tumor site; (II) regional recurrence/progression in the regional lymph nodes; (III) brain metastasis; (IV) extracranial distant organ metastasis and non-regional lymph node metastasis.

Statistical analysis

Counts and percentages were used to describe clinicopathological characteristics. The Kaplan-Meier method and log-rank tests were used to conduct univariate analyses and compare survival differences. Variables with $P<0.1$ in univariate analysis were included in the multivariate Cox regression model. Multivariate Cox regression survival analysis was performed to identify independent prognostic factors. All analyses were performed using the SPSS software (version 25.0, IBM, USA).

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee of Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, China (No. K2023-438-01) and informed consent was obtained from all individual participants.

Results

Patients' information and tumor characteristics are presented in *Table 1*. The age at diagnosis ranged from 42 to 85 years old. The mean and median ages were 59.4 and 59 years old, respectively. The majority of tumors (88.65%, 125/140) were located in the middle or lower thoracic esophagus, consistent with established epidemiological patterns reported in previous studies (5,14).

The median follow-up duration was 45.0 months [95% confidence interval (CI): 30.518–59.482] and the median OS was 24.0 months (95% CI: 19.391–28.609) for the entire cohort. The 1-, 3-, and 5-year OS rates were 79.3% (95% CI: 72.5–86.1%), 20.0% (95% CI: 13.3–26.7%), and

Table 1 Patients' information and tumor characters

Characteristic	No. of patients	Percentage
Sex		
Male	104	74.3
Female	36	25.7
Age		
≥60 years	67	47.9
<60 years	73	52.1
Smoking history		
Yes	56	40.0
No	84	60.0
Drinking history		
Yes	28	20.0
No	112	80.0
Pathology		
Pure SCCE	111	79.3
Combined carcinoma	29	20.7
Location		
Cervical	0	0
Upper thoracic	15	10.7
Middle thoracic	97	69.3
Lower thoracic	28	20.0
T category		
T1	15	10.7
T2	32	22.9
T3	66	47.1
T4	27	19.3
N category		
N0	35	25.0
N1	58	41.4
N2	34	24.3
N3	13	9.3
M category		
M0	107	76.6
M1	33	23.4
VALSG-stage		
LS	107	76.4
ES	33	23.6

Table 1 (continued)

Table 1 (continued)

Characteristic	No. of patients	Percentage
Chemotherapy		
Yes	122	87.1
No	18	12.9
Cycles of chemotherapy		
0	18	12.9
1 to <4	52	37.1
4 to ≤6	67	47.9
>6	3	2.1
Radiotherapy		
Yes	55	39.3
No	85	60.7
Dose of RT		
0	85	60.7
<55 Gy	24	17.1
≥55 Gy	31	22.1
Surgery		
Yes	84	60.0
No	56	40.0
Causes of PD		
No progress	62	44.3
Progress of PL or RNL	37	26.4
Metastasis	41	29.3
Effect evaluation [†]		
CR	77	55.0
PR	45	32.1
SD	13	9.3
PD	5	3.6

[†], evaluate the effectiveness after first line anti-tumor treatment according to RECIST 1.1. CR, complete response; ES, extensive stage; LS, limited stage; PD, progressive disease; PL, primary lesion; PR, partial response; RNL, regional lymph nodes; RT, radiotherapy; SCCE, small cell carcinoma of the esophagus; SD, stable disease; VALSG, Veterans Administration Lung Study Group.

9.3% (95% CI: 4.4–14.2%), respectively. After the first-line treatment, the ORR was 87.1% (122/140). By the endpoint of follow-up, 78 (55.7%) patients experienced disease progression. The pattern of first treatment failure

was meticulously analyzed. Local failure (primary lesion progression) occurred in 19 patients (24.4%), and regional failure (regional lymph node progression) was observed in 18 (23.1%). Distant metastasis was the most common mode of failure, identified in 41 patients (52.6%). Among these, 7 patients (9.0% of all progressions) presented with brain metastases, while 34 (43.6%) developed extracranial distant metastases. At the final follow-up, 86 deaths (61.4%) had occurred. The causes of death were rigorously reviewed and categorized. The vast majority of deaths (n=73, 84.9%) were directly attributed to disease progression. Treatment-related mortality was documented in 6 cases (7.0%), and 7 patients (8.1%) died from non-cancer-related causes.

Subsequent therapy after disease progression

Among the 78 patients who experienced disease progression, 72 (92.3%) received second-line therapy. The management strategies were diverse. A total of 57 patients received 2 to 4 cycles of chemotherapy. The most common chemotherapy regimen was irinotecan combined with platinum (n=48), followed by etoposide combined with platinum (n=9).

Among these 57 patients, the treatment modalities were further stratified: 17 patients received chemotherapy combined with palliative radiotherapy, 6 received chemotherapy combined with the targeted agent anlotinib, 3 received chemotherapy combined with immunotherapy, and 31 received chemotherapy alone.

Additionally, 15 patients received radiotherapy alone as their second-line treatment.

Prognostic factor analysis

Clinicopathological variables, including sex, age, smoking history, drinking history, pathology, location of carcinoma, TNM stage, chemotherapy, radiotherapy, surgery, and effect evaluation, were analyzed to evaluate the relationship between these variables and prognosis. Univariate analysis demonstrated that patients younger than 60 years had significantly longer median survival time (MST) (31.00 months) compared to older patients (21.00 months, $P=0.03$). Significant differences in survival were also observed according to N category ($P=0.03$) and M category ($P=0.042$), while T category showed borderline significance ($P=0.05$). Patients who received chemotherapy exhibited superior survival outcomes compared to those who did not (26 vs. 21 months, $P=0.01$). No other variables showed significant association with prognosis ($P>0.05$) (Table 2).

Table 2 Univariate overall survival analysis for the prognosis of 140 patients

Variable	No. of patients	MST (months, 95% CI)	χ^2	P value
Gender			0.201	0.65
Male	104	24 (17.456–30.544)		
Female	36	24 (17.792–30.208)		
Age			4.260	0.03
<60 years	73	31 (23.330–38.670)		
≥60 years	67	21 (18.489–23.511)		
Smoking history			0.511	0.47
Yes	56	25 (14.261–35.739)		
No	84	23 (17.233–28.767)		
Drinking history			0.020	0.88
Yes	28	21 (16.773–25.227)		
No	112	26 (19.910–32.090)		
Pathology			0.250	0.61
Pure SCCE	111	26 (19.140–32.860)		
Combined carcinoma	29	21 (14.214–27.786)		
Location			1.203	0.54
Upper thoracic	15	33 (19.980–46.020)		
Middle thoracic	97	24 (17.972–30.028)		
Lower thoracic	28	21 (14.370–27.630)		
T category			7.836	0.050
T1	15	40 (16.371–63.629)		
T2	32	59 (9.320–108.680)		
T3	66	22 (17.409–26.591)		
T4	27	21 (11.452–30.548)		
N category			8.826	0.03
N0	35	40 (23.979–56.021)		
N1	58	21 (18.685–23.315)		
N2	34	23 (16.304–29.696)		
N3	13	16 (8.053–23.947)		
M category			4.129	0.04
M0	107	28 (21.419–34.581)		
M1	33	19 (11.878–26.122)		
Chemotherapy			6.600	0.01
Yes	122	26 (18.764–33.236)		
No	18	21 (9.237–32.763)		

Table 2 (continued)

Table 2 (continued)

Variable	No. of patients	MST (months, 95% CI)	χ^2	P value
Radiotherapy			0.618	0.43
Yes	55	29 (19.658–38.342)		
No	85	22 (18.036–25.964)		
Dose of RT			1.175	0.55
0	85	22 (18.036–25.964)		
<55 Gy	24	26 (12.619–39.381)		
≥55 Gy	31	31 (23.183–38.817)		
Surgery			0.889	0.34
Yes	84	24 (16.980–31.020)		
No	56	24 (16.339–31.661)		
Effect evaluation			5.136	0.16
CR	77	25 (18.227–31.773)		
PR	45	22 (10.400–33.600)		
SD	13	29 (16.082–41.918)		
PD	5	9 (0.000–21.740)		

CI, confidence interval; CR, complete response; MST, median survival time; PD, progressive disease; PR, partial response; RT, radiotherapy; SCCE, small cell carcinoma of the esophagus; SD, stable disease.

Table 3 Multivariate Cox analysis for prognostic factors of overall survival

Variable	B	SE	Wald	P value	HR	95% CI
Age	0.242	0.234	1.071	0.30	1.274	0.805–2.015
T category	0.220	0.129	2.886	0.08	1.246	0.967–1.605
N category	0.194	0.127	2.339	0.12	1.214	0.947–1.556
M category	0.197	0.253	0.606	0.43	1.217	0.742–1.998
Chemotherapy	−0.656	0.331	3.943	0.047	0.519	0.271–0.992

CI, confidence interval; HR, hazard ratio; SE, standard error.

Five variables, including age, T category, N category, M category, and chemotherapy status were selected for multivariate Cox analysis. The multivariate analysis suggested that chemotherapy was an independent prognostic factor [hazard ratio (HR) 0.519; 95% CI: 0.271–0.992; $P=0.047$] (Table 3, Figure 2).

Treatment modality for limited stage SCCE (LS-SCCE)

Based on the multivariate analysis, chemotherapy was an independent prognostic factor of OS in patients with SCCE.

Undoubtedly, chemotherapy was the main treatment in patients with ES SCCE (ES-SCCE). However, the primary treatment modalities established for patients with LS-SCCE are surgery-based multimodal therapy [surgery (S) ± chemotherapy (CT) ± radiotherapy (RT)] and definitive CRT. Therefore, we performed a subgroup analysis of these treatment modalities in the LS-SCCE cohort. Among the 140 patients in the final study cohort, 107 were diagnosed with LS-SCCE. Of these, 76 patients underwent surgery-based multimodal therapy, and 25 received definitive CRT. The remaining six patients received monotherapy alone

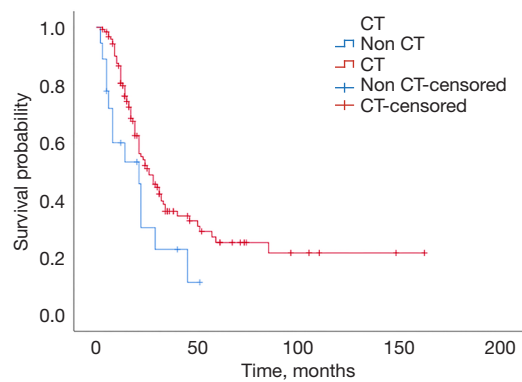


Figure 2 Cumulative survival rate curve of OS (CT *vs.* non-CT). CT, chemotherapy; OS, overall survival.

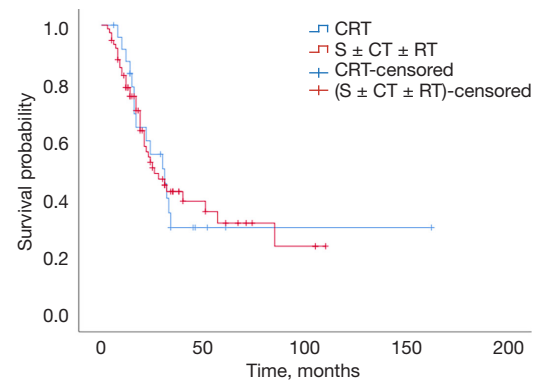


Figure 3 Cumulative survival rate curve of OS (S ± CT ± RT *vs.* CRT). CRT, chemoradiotherapy; CT, chemotherapy; OS, overall survival; RT, radiotherapy; S, surgery.

Table 4 Survival analysis of treatment modality for patients with LS-SCCE

Treatment group	PFS			OS		
	MST	χ^2	P	MST	χ^2	P
S ± CT ± RT	17.00 (9.77–24.23)	0.119	0.730	26.00 (16.09–35.91)	0.001	0.97
CRT	16.00 (11.52–20.48)			31.00 (19.84–42.16)		

CRT, chemoradiotherapy; CT, chemotherapy; LS-SCCE, limited stage small cell carcinoma of the esophagus; MST, median survival time; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; S, surgery.

(chemotherapy alone, n=3; radiotherapy alone, n=3) due to poor performance status and intolerance to both surgery and CRT. To ensure a robust and clinically relevant comparison between curative-intent strategies, these six patients receiving monotherapy were excluded from the subsequent survival analysis. Consequently, a formal comparative survival analysis was conducted between the surgery-based multimodal therapy group (n=76) and the definitive CRT group (n=25). Analysis of different treatment approaches for limited-stage SCCE revealed distinct clinical outcomes. The median OS was 26 months for patients receiving surgery-based multimodal therapy compared to 31 months for those receiving definitive CRT (P=0.97). Similarly, the median PFS was 17 months for the surgery-based multimodal therapy group *vs.* 16 months for the definitive CRT group (P=0.73). Notably, both multimodal therapeutic strategies demonstrated comparable efficacy, with no statistically significant differences observed in either OS or PFS between the two treatment approaches. These findings suggest that definitive CRT may represent a viable alternative to surgery-based multimodal therapy for patients with limited-stage SCCE (Table 4, Figures 3,4).

Discussion

SCCE is a malignant tumor of the digestive tract with a low incidence (15-17), however, it is highly malignant, characterized by early metastatic spread and poor prognosis. Owing to its unique clinical characteristics, no prospective clinical studies have been conducted, and there is a lack of clear consensus on the treatment regimen and prognostic factors. While many studies on SCCE are retrospective in nature, they are often associated with some limitations and drawbacks. First, their sample size was generally small, and most studies had only a few dozen of cases or less (2,18-20). Second, several studies with large sample sizes were based on database information, such as the Surveillance Epidemiology and End Results (SEER) database (4,21-23). However, because these cases came from multiple medical centers, there were some limitations such as incomplete basic information, selection bias, and inconsistent treatment methods. We reviewed 15-year SCCE cases at our center, with a sample size of 140 patients. All cases in this study were diagnosed and managed at our institution, ensuring comprehensive clinical documentation and standardized

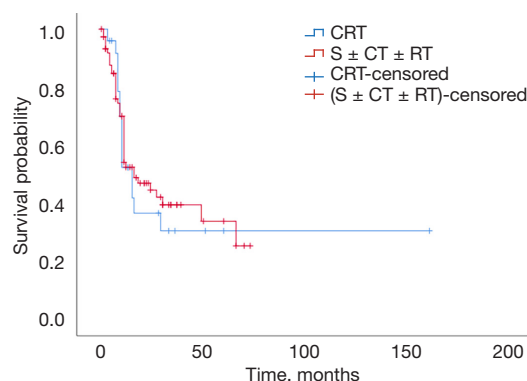


Figure 4 Cumulative survival rate curve of PFS ($S \pm CT \pm RT$ vs. CRT). CRT, chemoradiotherapy; CT, chemotherapy; PFS, progression-free survival; RT, radiotherapy; S, surgery.

treatment protocols. This included consistent chemotherapy regimens, precisely defined radiotherapy target volumes and dosage parameters, as well as uniform surgical approaches. In this study, the clinical characteristics and prognostic factors of SCCE were analyzed, particularly the treatment of LS-SCCE, which remains controversial, with the ultimate objective of informing standardized treatment protocols.

SCCE occurs primarily in the elderly population. The median age at diagnosis in our cohort was 59 years, consistent with previous reports ranging from 58.8 to 67 years (7,24,25). A nationwide clinicopathological analysis encompassing 582 hospitals across 32 Chinese provinces reported a median age of 60 years for SCCE patients in China (16). Our cohort was stratified by age into two groups: <60 years ($n=73$) and ≥ 60 years ($n=67$). Comparative survival analysis revealed 1-, 3-, and 5-year OS rates of 80.82%, 26.03%, and 13.70% respectively for younger patients (<60 years), vs. 79.1%, 13.43%, and 4.48% for older patients (≥ 60 years). While univariate analysis demonstrated a statistically significant difference in MST (31.0 vs. 21.0 months, $P=0.03$), multivariate analysis failed to identify age as an independent prognostic factor for OS. These findings are consistent with the majority of published SCCE studies (5,25,26). Notably, only a single published study has identified advanced age as an independent predictor of poor survival in SCCE (22). However, the mean age of that study was 68.6 ± 11.8 years, which was older than that of other studies, which might have affected the analysis results.

Our study demonstrated that the middle and lower esophagus were the primary tumor sites in 89.3% of cases

(125/140), consistent with previous reports (3,17,26,27). However, there was no clear explanation for this finding. One plausible hypothesis involves tumor origin from amine precursor uptake and decarboxylase (APUD) cell (28), which are often found in the distal esophagus (29). Therefore, the middle and lower esophagus are the most common sites for SCCE. Another hypothesis is that SCCE is related to Merkel cells, which are abundant neuroepithelial cells in the middle esophageal area (30).

SCCE carries a particularly poor prognosis, as evidenced by multiple clinical studies. The current analysis demonstrates a median OS of 24.0 months (95% CI: 19.391–28.609) with corresponding 1-, 3-, and 5-year survival rates of 79.3%, 20.0%, and 9.3%, respectively. These findings align with previous reports, including Miao *et al.*'s retrospective analysis of 113 SCCE cases showing a MST of 22.9 months with 1- and 3-year OS rates of 45% and 12% (25), and Jeene *et al.*'s study reporting an MST of 16 months and survival rates of 65%, 30%, and 22% at 1, 3, and 5 years respectively (2). The uniformly dismal long-term outcomes observed across studies likely reflect the intrinsic biological aggressiveness of small cell carcinomas, characterized by rapid proliferation, early metastatic spread, and frequent disease recurrence. This pattern mirrors that seen in other small cell malignancies, including SCLC, where reported MST ranges from 10–17 months depending on disease stage (31–34), with 5-year survival rates consistently below 10% (35). Similarly, extrapulmonary small cell carcinomas demonstrate comparably poor outcomes, with MST ranging from 3–27 months and 5-year survival rates approximating 13% (36–39). Distant metastasis represents the predominant mode of treatment failure in SCCE. In our cohort, 78 patients (55.7%) experienced disease progression following first-line therapy, with distant metastases accounting for 52.6% (41/78) of these cases. This pattern of systemic dissemination is consistent with Miao *et al.*'s findings, where 31.0% of patients developed recurrence or metastases, with distant sites involved in 77.1% (27/35) of these cases (25). The high frequency of metastatic spread underscores the need for effective systemic therapies in SCCE management.

Chemotherapy has always played a very important role in the treatment of various small cell tumors because of its aggressive nature and ease of metastasis. Our multivariate Cox regression analysis identified chemotherapy as a significant independent prognostic factor for OS in SCCE (HR, 0.519; 95% CI: 0.271–0.992; $P=0.047$). These findings corroborate existing literature, including Li *et al.*'s report of chemotherapy as an independent predictor of

cancer-specific survival (21) and SEER database analyses confirming its prognostic significance (22). Although standardized treatment protocols for SCCE have not been established, chemotherapy is universally recognized as the mainstay of treatment for extensive-stage disease (ES-SCCE) and constitutes an essential element of combined modality therapy for LS-SCCE.

Despite the poor long-term survival, we noted that SCCE was sensitive to first-line treatment. In our study, the ORR after first-line treatment was 87.1% (122/140). This robust treatment response highlights the critical importance of optimal initial therapeutic strategy selection, particularly for patients with limited-stage disease who may achieve definitive disease control. However, the management of LS-SCCE remains subject to clinical controversy regarding the choice between surgical and non-surgical local treatment modalities. Therefore, we performed a subgroup analysis to compare surgery-based multimodal therapy and definitive CRT in patients with LS-SCCE. Wang's retrospective study reported superior survival outcomes with multimodal therapy compared to monotherapy (15.5 *vs.* 9.3 months, $P=0.02$) (18). However, it is controversial whether surgery-based multimodal therapy ($S \pm CT \pm RT$) or definitive CRT is the preferred treatment modality. Our study revealed no significant difference in outcomes between patients with LS-SCCE who received and those treated with definitive CRT (26 *vs.* 31 months, $P=0.976$). It suggested that CRT might be recommended as first-line treatment for patients with LS-SCCE, especially for those patients who were intolerant of surgery or unwilling to undergo surgery (40). These findings were further corroborated by an independent study demonstrating comparable overall and recurrence-free survival outcomes between patients receiving CRT and those undergoing surgery with adjuvant therapy ($P>0.05$) (41), providing external validation of our results. In the study by Yan *et al.* focusing on LS-SCCE, no significant survival difference was observed between patients undergoing surgery-based multimodal therapy and those receiving definitive CRT. Notably, definitive CRT was associated with significantly improved OS compared to surgery in patients older than 60 years (median OS: 36.0 *vs.* 20.9 months, $P=0.007$) (42).

We acknowledge the inherent limitations of this study. Firstly, its retrospective nature over a 15-year period introduces potential biases, including selection bias and heterogeneity in diagnostic and therapeutic approaches that may have evolved over time. Secondly, although this is one of the largest single-institution studies on SCCE, the

sample size, particularly in subgroup analyses (e.g., the CRT group for LS-SCCE), remains relatively small, which may limit the statistical power to detect significant differences. Finally, treatment strategies were not randomized but were determined by multidisciplinary team discussion based on individual patient and disease characteristics, which could lead to confounding by indication. Despite these limitations, our findings provide valuable insights into the management of this rare malignancy.

Conclusions

Cox multivariate regression analysis suggested that chemotherapy is an independent prognostic factor for SCCE. According to the LS-SCCE analysis, patients who received multimodal therapy had longer OS and PFS than those who underwent chemotherapy alone. However, there was no significant difference in OS and PFS between surgery-based multimodality therapy and CRT, suggesting that CRT might be an effective first-line treatment for LS-SCCE and is not inferior to surgery. Our study was retrospective, and the conclusions are expected to provide a reference for the standardized treatment of SCCE. In the future, larger case-prospective studies are needed to provide high-level evidence for evidence-based medicine in the standardized treatment of SCCE.

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Footnote

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uniform disclosure form (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-2025-414/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee of Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, China (No. K2023-438-01) and informed consent was obtained from all individual participants.

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