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The role of radiotherapy in small cell carcinoma of the esophagus: a retrospective study

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Abstract

Background Primary small cell carcinoma of the esophagus (SCCE) is an aggressive carcinoma with a rare incidence. Most patients were diagnosed with stage III-IV and have a poor prognosis. The poor therapeutic outcomes of SCCE reveal the need for more rational therapies.

Methods We retrospectively reviewed 15,463 patients with esophageal carcinoma from January 2015 to December 2020. 235 (1.52%) patients were pathologically diagnosed with primary SCCE. Clinical characteristics and treatment information were extracted from medical records. All statistical analyses were performed with the SPSS software. Patients were divided into radiotherapy (RT) group and non-RT group. The chi-square test was conducted to analyze the difference in baseline characteristics and propensity score matching (PSM) was used to balance the patient characteristics. Univariate and multivariate analysis was used to identify independent prognostic factors and calculated the estimated hazard ratio (HR) and 95% confidence interval (CI). The Kaplan-Meier method was used to draw survival curves, calculate the median overall survival (OS), and compare prognosis between groups with the log-rank *p* test. The two-tailed *p* value less than 0.05 indicated a significant difference.

Results The median OS was 15.2 months (range:13.4–17.1 months). The addition of RT improved median OS from 14.3 months to 16.5 months, but the difference was not statistically significant ($p=0.657$). After PSM, the median OS of the RT group was longer than the non-RT group (16.5 months vs. 11.5 months, $p<0.001$). Multivariate analysis identified RT (HR: 0.711, 95%CI: 0.533–0.949, $p=0.020$), surgery (HR: 0.490, 95%CI: 0.365–0.660, $p<0.001$), and smoking history (HR: 1.335, 95%CI: 1.010–1.765, $p=0.042$) as independent prognostic factors. Subgroup analysis showed that RT was not a prognostic factor in patients with surgery ($p=0.450$), but could significantly improve OS in patients without surgery (HR: 0.585, 95%CI: 0.415–0.824, $p=0.002$). Both middle and lower thoracic SCCE patients could benefit from the addition of RT. RT could improve OS regardless of Ki67 expression level. Subgroup analyses also indicated that stage IV, age ≥ 60, no smoking history, pure SCCE, Syn-positive, CgA-positive, CD56-positive patients could benefit from RT.

Conclusions SCCE patients could benefit from RT, especially those without surgery. Further studies are required for confirmation of the conclusion.

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Keywords Small cell carcinoma of the esophagus, Radiotherapy, Chemotherapy, Surgery

Introduction

Primary small cell carcinoma of the esophagus (SCCE) is an aggressive and rare carcinoma with a poor prognosis. The incidence only accounts for 0.4–2.8% of all histological types of esophageal cancer [1, 2]. Epidemiological data show that SCCE is more likely to occur in men and is usually located in the middle part of the esophagus in China or in the lower part in Western countries [3, 4]. Due to its highly invasive and metastatic features, many patients are advanced-stage when diagnosed. Most patients recur within one year of initial treatment and die after a few months. Their median overall survival (OS) time is only 7 to 28 months, and the 5-year OS rate is just 6.7-18% [5–8].

Pathology is the gold diagnosis standard for SCCE, including simple small-cell carcinoma and mixed small-cell carcinoma. From the limited case reports, synaptophysin (Syn), neuronal cell adhesion molecules (CD56), neuron-specific enolase (NSE), and chromogranin A (CgA) were reported as common immunohistochemical biomarkers for SCCE [9–11]. Due to the low incidence and poor prognosis of SCCE, it is difficult to carry out large-scale randomized controlled trials to establish standard treatment options. SCCE is usually treated based on the guidelines for small cell lung carcinoma (SCLC) because of their histologic similarities.

For patients with limited-stage SCLC, the standard of care is platinum-based chemotherapy (CT) concurrent with thoracic radiotherapy (TRT) according to the National Comprehensive Cancer Network (NCCN) [12]. There is also a role for surgery and adjuvant chemotherapy in patients with very early-stage SCLC (T1-2N0M0) [12]. Prophylactic cranial irradiation (PCI) is also recommended to patients responsive to initial treatments. With the development of immune-checkpoint inhibitors (ICIs), the combination of platinum-based chemotherapy and durvalumab or atezolizumab has been approved as the new standard for the first-line treatment for extensive-stage SCLC patients [12].

TRT and PCI also recommended in selected limited-stage SCLC patients to enhance local control and lead to favored the long-term survival.

Radiation is not only an important local treatment in SCLC, but only in non-small esophageal carcinoma (EC). In locally advanced non-small EC patients, neoadjuvant chemoradiotherapy (CRT) and surgery (S) are the gold standard for resectable patients and definitive concurrent CRT were recommended to inoperable ones [13]. As for advanced EC patients, systemic chemotherapy has been a normal choice. Some retrospective studies has reported that radical radiation to metachronous oligometastatic sites led to a modest increase in progression free survival (PFS) and OS compared with chemotherapy alone [14, 15]. Stronger evidence from a randomized, multicenter, phase 2 clinical trial (NCT03904927) showed that the addition of local treatment (radiotherapy (RT), surgery, or thermal ablation) for metastases could improve PFS from 6.4 months to 15.3 months for oligometastatic esophageal squamous cell carcinoma (ESCC) patients (HR:0.26, 95%ci:0.14–0.42, $p < 0.0001$) [16]. Hence, RT is also useful in selected advanced EC patients.

It is not feasible to perform prospective randomized controlled trials (RCTs) on SCCE, most were retrospective studies. Based on the published studies, RT were more used in western countries than China [3–5, 7]. Some retrospective studies have indicated that the addition of RT to chemotherapy or surgery could improve prognosis of SCCE patients [3, 4, 8, 17–20]. A most large-scale, multicenter, retrospective cohort study with 458 limited-stage SCCE patients found that the addition of RT (hazard ratio (HR): 0.57, 95% confidence interval (CI): 0.41–0.8, $p = 0.001$) could improve OS compared with chemotherapy alone [21].

However, studies focused on RT are still lacked, especially in advanced SCCE. The role of RT has not been clearly illustrated so far. We performed this retrospective study to summarize the characteristics and treatment of SCCE patients and focus on the role of RT in improving the prognosis.

Methods

Patients and methods

We retrospectively reviewed 15,463 EC patients in our institution from January 2015 to December 2020. Among them, 235 (1.52%) patients were pathologically diagnosed with primary SCCE. The study was conducted following the Declaration of Helsinki and was approved by the hospital ethics committee. All patients signed informed consent at admission.

Inclusion and exclusion criteria

The patients selected for this study meet the following inclusion criteria: [1] pathological diagnosed as SCCE by gastroscope or surgery specimen [2], no mixed with other malignant tumors [3], complete medical records. Patients who met the following conditions were excluded from the study: [1] coexistence of other malignancies [2], incomplete medical records, and [3] non-tumor-related deaths.

Data collection

Clinical characteristics and treatment information were extracted from medical records. Patients were staged according to the 8th edition of the tumor, nodes, and metastases (TNM) staging system of the American Joint Committee on Cancer (AJCC) for EC.

Statistical analysis

All statistical analyses were performed using the SPSS software version 25.0 (IBM Corp, Armonk, NY, USA). OS was defined as the time from diagnosis to follow-up death or last follow-up. Patients alive or lost to follow-up were censored at the date of last follow-up. The chi-square test was conducted to analyze the difference in baseline characteristics between every two groups. Univariate and multivariate analysis with the Cox proportional hazard regression model was used to identify independent prognostic factors and calculated the estimated HR and 95% CI. Propensity score matching (PSM) was used to account for differences in patient characteristics among the two groups. The Kaplan-Meier method was used to draw survival curves, calculate the median survival time, and compare prognosis between groups with the log-rank p test. The two-tailed p value less than 0.05 indicated a significant difference.

Results

Patient characteristics

The clinical features of enrolled patients are in Table 1. The number of patients diagnosed between 2015 and 2020 was 24, 40, 34, 48, 38 and 51, respectively. The median age at diagnosis was 65 years (ranging from 37 to 85 years), and more older patients were diagnosed and treated in recent years (Fig. 1A). Most tumors were

Table 1 Clinical characters before and after matching

	n (%)	Before PSM			After PSM		
		RT (*n* = 100)	Non-RT (*n* = 135)	*P*	RT (*n* = 100)	Non-RT (*n* = 100)	*P*
Gender							
Male	157 (66.8%)	66	91	0.821	66	61	0.463
Female	78 (33.2%)	34	44		34	39	
Age	65 (range: 37–85)						
≥ 60	160 (68.1%)	66	94	0.555	66	74	0.217
< 60	75 (31.9%)	34	41		34	26	
Smoking history							
Yes	93 (39.6%)	36	57	0.335	36	41	0.467
No	142 (60.4%)	64	78		64	59	
Tumor location							
Cervical	2 (0.8%)	1	1	0.093	1	1	0.729
Upper thoracic	26 (11.1%)	15	11		15	10	
Middle thoracic	102 (43.3%)	44	58		44	44	
Lower thoracic	105 (44.7%)	40	65		40	55	
Stage							
T							
1	35 (14.9%)	11	24	0.207	11	14	0.239
2	51 (21.7%)	18	33		18	27	
3	115 (48.9%)	54	61		54	49	
4	34 (14.5%)	17	17		17	10	
N							
0	61 (26.0%)	22	39	0.234	22	23	0.866
1–3	174 (74.0%)	78	96		78	77	
M							
0	165 (70.2%)	75	90	0.167	70	64	0.112
1	70 (29.8%)	25	45		25	36	
TNM stage							
I	27 (11.5%)	6	21	0.039	6	13	0.342
II	38 (16.2%)	16	22		16	14	
III	60 (25.5%)	32	28		32	26	
IV	110 (46.8%)	46	64		46	47	
Surgery							
Yes	95 (40.9%)	28	67	0.001	28	40	0.073
No	140 (59.1%)	72	68		72	60	

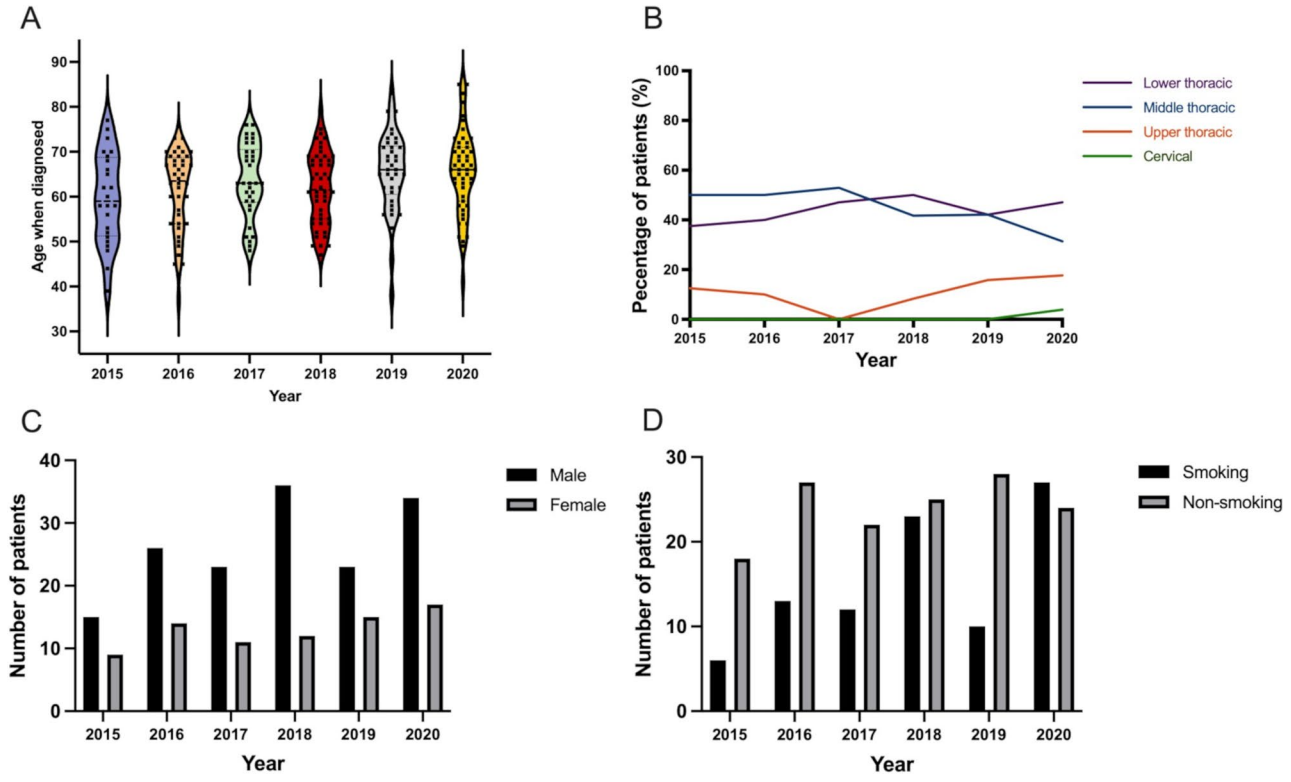

Fig. 1 From 2015 to 2020, (**A**) the age when diagnosed, the change of (**B**) tumor location, (**C**) male vs. female, and (**D**) smoking vs. non-smoking patients

Table 2 Pathological characters of enrolled patients

	n	Percentage (%)
Pathology		
Pure Small cell	208	88.5
Mixing with SCC	22	9.4
Mixing with ADC	5	2.1
Ki67%		
≤ 80%	150	63.8
> 80%	85	36.2
Syn		
Positive	195	83.0
Negative	40	17.0
CgA		
Positive	155	
Negative	80	
CD56		
Positive	209	88.9
Negative	26	11.1

detected in the middle thoracic (43.4%) or lower thoracic (44.7%). Between 2015 and 2017, the middle thoracic was the most common site for SCCE (Fig. 1B). However, the proportion of tumors in the lower thoracic gradually increased and became the predominant location of SCCE after 2018. The male-to-female ratio remained constant at approximately 2:1 (Fig. 1C). 39.6% of patients had a smoking history, and the proportion increased annually (Fig. 1D).

When diagnosed, patients with T1, T2, T3, and T4 stages accounted for 14.9%, 21.7%, 48.9% and 14.5%, respectively. Regarding the *N* stage, 74.0% of patients had positive lymph nodes. 110 (46.8%) patients were classified with stage IV, and of those, 70 patients (63.6%) had distant metastasis, including liver, distant lymph nodes (7.7%), bone (5.5%), lung (4.3%), brain (2.1%), adrenal gland (0.9%), spleen (0.4%), and thyroid gland (0.4%). The remaining patients were stage I ($n = 27$, 11.5%), stage II ($n = 38$, 16.2%) and stage III ($n = 60$, 25.2%).

Pathological characteristics

The pathological characteristics are listed in Table 2. The majority of patients (89.4%) were pure small cell esophageal carcinoma. We observed 20 patients with a combination of squamous cancer cell (SCC) and five patients with adenocarcinoma (ADC). In this study, Ki67, Syn, CgA, and CD56 were common indicators for SCCE. Among the patients with corresponding data of these indicators, Ki67 levels ranged from 30 to 95%, with 48.9% of patients demonstrating high expression (defined as ≥ 80%). Syn-positive patients accounted for 83.0%, CgA-positive patients for 21.7%, and CD56-positive patients for 88.9%.

Table 3 The first-line treatment selection by stage

First-line treatment	*n* = 235	Stage I (*n* = 27)	Stage II (*n* = 38)	Stage III (*n* = 60)	Stage IV (*n* = 110)
CT	83 (35.3%)	0	4 (10.5%)	12 (19.9%)	67 (60.9%)
RT	7 (3.0%)	0	2 (5.2%)	2 (3.4%)	3 (2.7%)
CRT	52 (22.1%)	0	5 (13.2%)	20 (33.3%)	27 (24.5%)
Surgery	20 (8.5%)	8 (29.6%)	5 (13.2%)	4 (6.7%)	3 (2.7%)
S + CT	68 (28.9%)	18 (66.7%)	21(55.3%)	21(35.0%)	8 (7.3%)
S + RT	1(0.5%)	0	0	1 (1.7%)	0
S + CRT	4 (1.7%)	1 (3.7%)	1 (2.6%)	0	2 (1.8%)

Table 4 The role of radiotherapy in enrolled patients

	Stage I (*n* = 27)	Stage II (*n* = 38)	Stage III (*n* = 60)	Stage IV (*n* = 110)
Radiotherapy (*n* = 100)	6	16	32	21
Early intervention (*n* = 64)	1	8	23	32
RT (*n* = 7)	0	2	2	3
CRT (*n* = 52)	0	5	20	27
S + CRT (*n* = 4)	1	1	0	2
S + RT (*n* = 1)	0	0	1	0
After progression (*n* = 36)	5	8	9	14
CT + R (*n* = 15)	0	0	4	11
S + R (*n* = 6)	3	2	1	0
S + CT + R (*n* = 15)	2	6	4	3

First-line treatment options

Treatment options for SCCE patients included chemotherapy, RT, surgery, immunotherapy, anti-angiogenic therapy, and their combinations. All the patients received chemotherapy during their disease course, with etoposide and platinum being the most commonly used regimens. As regard to anti-angiogenic therapy, anlotinib and apatinib were administered. Immunotherapy employed were durvalumab, sintilimab, camrelizumab, and tislelizumab.

As first-line treatment, CRT was conducted in 52 (22.1%) patients. 83 (35.3%) patients received chemotherapy alone. RT was the only first-line treatment in seven patients (3.0%), while 20 patients (8.5%) had surgery alone. 68 patients (28.9%) received S + CT, whereas only one patient (0.5%) received S + R, and four patients (1.7%) underwent S + CRT.

The first-line treatment in patients with different stages are shown in Table 3. All the stage I patients were treated with surgery, including 18 (66.7%) patients with S + CT, eight (29.6%) patients with surgery alone, and only one patients (3.7%) with S + CRT. In the stage II patients, 27 (71.1%) patients conducted surgery (S + CT: *n* = 21; S + CRT: *n* = 5; surgery alone: *n* = 1). The remaining five (13.2%) patients received CRT, and four (10.5%) patients with chemotherapy and two (5.2%) patients with RT alone. As for stage III patients, 23 (38.4%) patients received RT (CRT: *n* = 20; RT: *n* = 2; S + RT: *n* = 1) and 12 (19.9%) patients were treated with chemotherapy alone. 26 (42.4%) patients performed surgery (S + CT: *n* = 21; S + RT: *n* = 1; surgery alone: *n* = 4). In stage IV patients, 67 (60.9%) patients were treated with chemotherapy alone, 27 (24.5%) patients with CRT and three (2.7%) patients with RT alone. Eleven (27.5%) patients received surgery for metastasis as first-line treatment (S + CT: *n* = 8, S + CRT: *n* = 2; surgery alone: *n* = 3).

Radiotherapy in different stages

Throughout the course of disease, 100 patients received RT, of which 64.0% occurred prior to disease progression (Table 4). RT was most commonly used in patients with stage III (53.3%) and stage IV (41.8%) disease. In stage I, one patient received S + RT and five patients received RT after progression. In stage II, seven patients received RT (± CT), one received S + RT and eight patients received RT after progression. In stage III, 22 patients received RT (± CT), one patients received S + RT, and nine patients received RT after progression. In stage IV, 30 patients received RT (± CT), two patients received S + CRT, and 14 patients received RT after progression. No patient received PCI in our study.

Overall survival

The median follow-up in this study was 15.2 months, ranging from 1.3 months to 87.3 months. The OS rates at 1-, 2-,3-, and 5-years were respectively 63.4%, 28.9%, 20.4% and 6.0%. The median OS was 15.2 months (95% CI:13.4–17.1 months) in the entire population. The median OS were 32.3 months in stage I, 19.4 months in stage II, 15.2 months in stage III, and 12.5 months in stage IV, respectively (Fig. 2A).

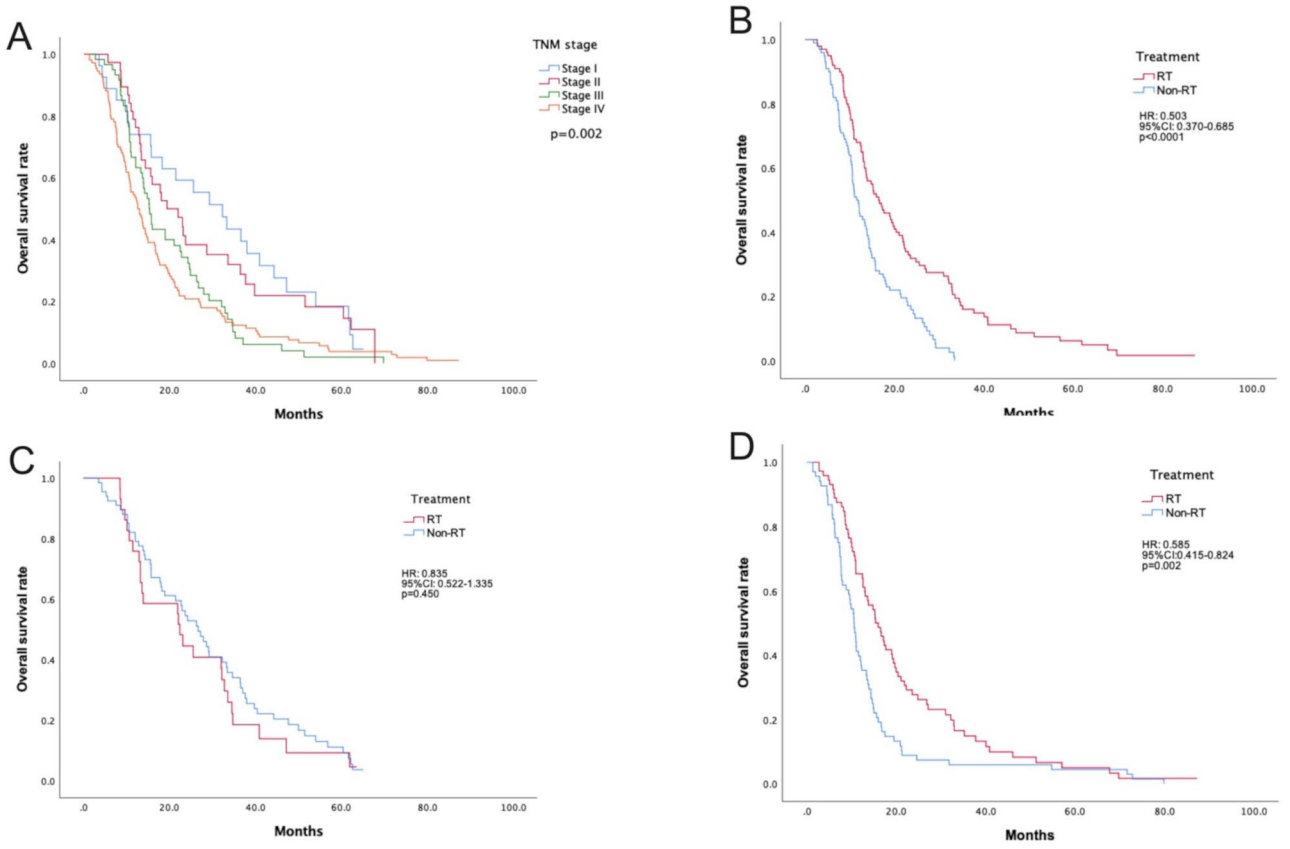

Fig. 2 The overall survival rate of (**A**) patients of different stage, and the comparison of overall survival rate between RT group and non-RT group in (**B**) entire patients, (**C**) in patients with surgery and (**D**) in patients without surgery

Table 5 Univariate analysis and multivariate Cox regression for prognostic factors

	HR	95%CI	*P*	HR	95%CI	*P*
Age (≥ 60 vs. <60)	**1.385**	**1.037–1.848**	**0.027**			
Gender (Male vs. Female)	0.998	0.752–1.325	0.991			
Smoking history (Yes vs. No)	**1.343**	**1.020–1.769**	**0.036**	1.335	1.010–1.765	0.042
Comorbidity (Yes vs. No)	1.156	0.890–1.532	0.314			
Ki67 (≤ 80%> vs. 80%)	0.905	0.788–1.039	0.156			
Syn (Positive vs. Negative)	1.340	0.936–1.919	0.110			
CgA (Positive vs. Negative)	1.207	0.576–1.352	0.566			
CD56 (Positive vs. Negative)	0.883	0.576–1.352	0.566			
Surgery (Yes vs. No)	**0.544**	**0.412–0.718**	**< 0.001**	0.490	0.365–0.660	< 0.001
Radiotherapy (Yes vs. No)	**0.941**	**0.720–1.231**	**0.657**	0.711	0.533–0.949	0.020
Immunotherapy (Yes vs. No)	0.820	0.506–1.330	0.422			
Anti-angiogenic (Yes vs. No)	0.958	0.625–1.469	0.843			
Tumor location (Middle thoracic vs. Others)	0.915	0.701–1.195	0.514			
TNM stage (I-II vs. III-IV)	**0.671**	**0.513–0.877**	**0.003**			

Note: Data in bold are included in the multivariate analysis

Prognostic factors

Univariate cox regression analysis was used to analyses typical clinical factors, pathological markers, and treatment options. Age ($p = 0.027$), smoking history ($p = 0.036$), surgery ($p < 0.001$), and TNM stage ($p = 0.003$) emerged as potential prognostic factors in the whole sample (Table 5). The significant factors along with RT ($p = 0.657$) were enrolled for multivariate analysis. RT (HR: 0.711, 95% CI: 0.533–0.949, $p = 0.020$), surgery (HR: 0.490, 95% CI: 0.365–0.660, $p < 0.001$), and smoking history (HR: 1.335, 95% CI: 1.010–1.765, $p = 0.042$) were identified as independent prognostic factors in this study (Table 5).

The role of RT

To investigate the role of RT, patients were divided into two groups: RT group ($n = 100$) and non-RT group ($n = 135$). The median OS increased from 14.3 months in the non-RT group to 16.5 months in the RT group, but the difference was not statistically significant ($p = 0.657$) (Fig. 2B). There was a significant difference in TNM stage ($p = 0.039$) and percentage of surgical treatment ($p = 0.001$) between the RT group and non-RT groups (Table 1). To balance the clinical characteristics, PSM was used and 100 patients were finally enrolled in each group. No significant differences were found between the clinical factors of the two groups after PSM (Table 1). The median OS of the RT group was improved from 11.5 months to 16.5 months compared to the non-RT group (HR: 0.503, 95% CI: 0.370–0.685, $p < 0.001$).

Subgroup analysis

To better identify patients who would benefit from RT, we performed multivariate cox regression analysis in different subgroups. First, patients were divided according to whether they underwent surgery or not. Of the 95 patients who were treated with surgery, only four patients received RT with surgery, other 25 patients received RT after progression. The median OS was 24.2 months (95% CI: 19.6–28.9 months) and RT was not a prognostic factor in these patients (HR: 0.835, 95% CI: 0.522–1.335, $p = 0.450$) (Fig. 2C). Within the 140 patients without surgery, median OS was 12.4 months (95% CI: 10.2–14.6 months). RT was used in 71 patients and most received early intervention. Only 15 patients received RT after progression. OS was significantly improved from 10.5 months to 15.3 months (HR: 0.585, 95% CI: 0.415–0.824, $p = 0.002$) compared to non-RT patients (Fig. 2D).

The results of the subgroup analyses are summarized in Fig. 3. Middle and lower thoracic SCCE patients could both benefit from the addition of RT. RT could improve OS regardless of the expression level of Ki67. Subgroup analyses also revealed that stage IV, age ≥ 60, no smoking history, pure SCCE, Syn-positive, CgA-positive, CD56-positive patients could benefit from RT.

Discussion

As an aggressive carcinoma with a poor prognosis and no consensus on treatment regimens, SCCE has always been a major challenge. It is crucial to gain insight into the therapeutic options and prognosis of SCCE patients in the real world.

From 2015 to 2020, 235 primary SCCE patients were diagnosed at our institution, of which 46.8% were stage IV. The incidence rate of SCCE in our study was 1.52%, which is consistent with previous reports (0.4-2.0%) [1–4]. The median OS was 15.3 months and the 5-year OS rate was 6.0%, which was also similar to previous reports [5–8]. The primary site of SCCE in the Chinese population was most frequently reported in the middle thoracic, whereas the US population has a higher incidence in the middle region [3, 4]. It's interesting to note that our study shows a recent changing trend in the location of SCCE, shifting towards the lower esophagus.

As two important local treatments, surgery and RT have been used in patients with different clinical characteristics. In contrast to Western countries, surgery is more commonly used than RT for localized SCCE in China [3–5, 7, 17]. in the previous retrospective studies of Chinese SCCE patients, only 19.4–26.7% of patients underwent RT (18–19). However, the most recent results reported that RT was used in 40.9% of SCCE patients [17], which is similar with the 42.5% at our institution, indicating that RT is increasingly being used to treat SCCE in China.

Compared to previous studies, our study involved the most recent SCCE patients, and a significant proportion of patients received RT. RT (HR: 0.711, 95%CI: 0.533–0.949, $p = 0.020$) and surgery (HR: 0.490, 95%CI: 0.365–0.660, $p < 0.001$) were identified as independent prognostic factors. Our study found that inoperable patients could benefit from RT (15.3 months vs. 10.5 months; HR: 0.585, 95%CI: 0.415–0.824, $p = 0.002$). In patients with surgery, however, RT did not confer a survival benefit (HR: 0.835, 95% CI: 0.522–1.335, $p = 0.450$).

An analysis of SCCE patients who underwent surgical intervention from the Surveillance, Epidemiology, and End Results Program (SEER) database demonstrated that preoperative RT could improve prognosis, but postoperative RT could not [4]. Therefore, the efficacy of preoperative RT, postoperative RT, and RT after progression may be completely different.

In patients with surgery in our study, RT after progression were mostly used, which is different in the group of patients without surgery. The weaker role of RT in patients with surgery may be caused by the different timing of RT.

For non-metastatic patients, S + CT, S + CRT, CRT, or chemotherapy are possible treatment options. The multicenter clinical trial, ChiSCEC, reported that both surgery and CRT are suitable treatment options for patients with limited-stage SCCE. There were no significant differences in survival between S + CT and CRT groups ($p > 0.05$) and both were better than chemotherapy alone [21]. Preoperative or postoperative RT was not involved in the ChiSCEC study and was very limited in our study. The combination of RT with surgery still needs further studies and more detailed subgroup analysis. The role of RT in surgical patients may be more important than the currently reported results.

Previous studies have highlighted the importance of RT in patients with limited-stage SCCE. However, advanced

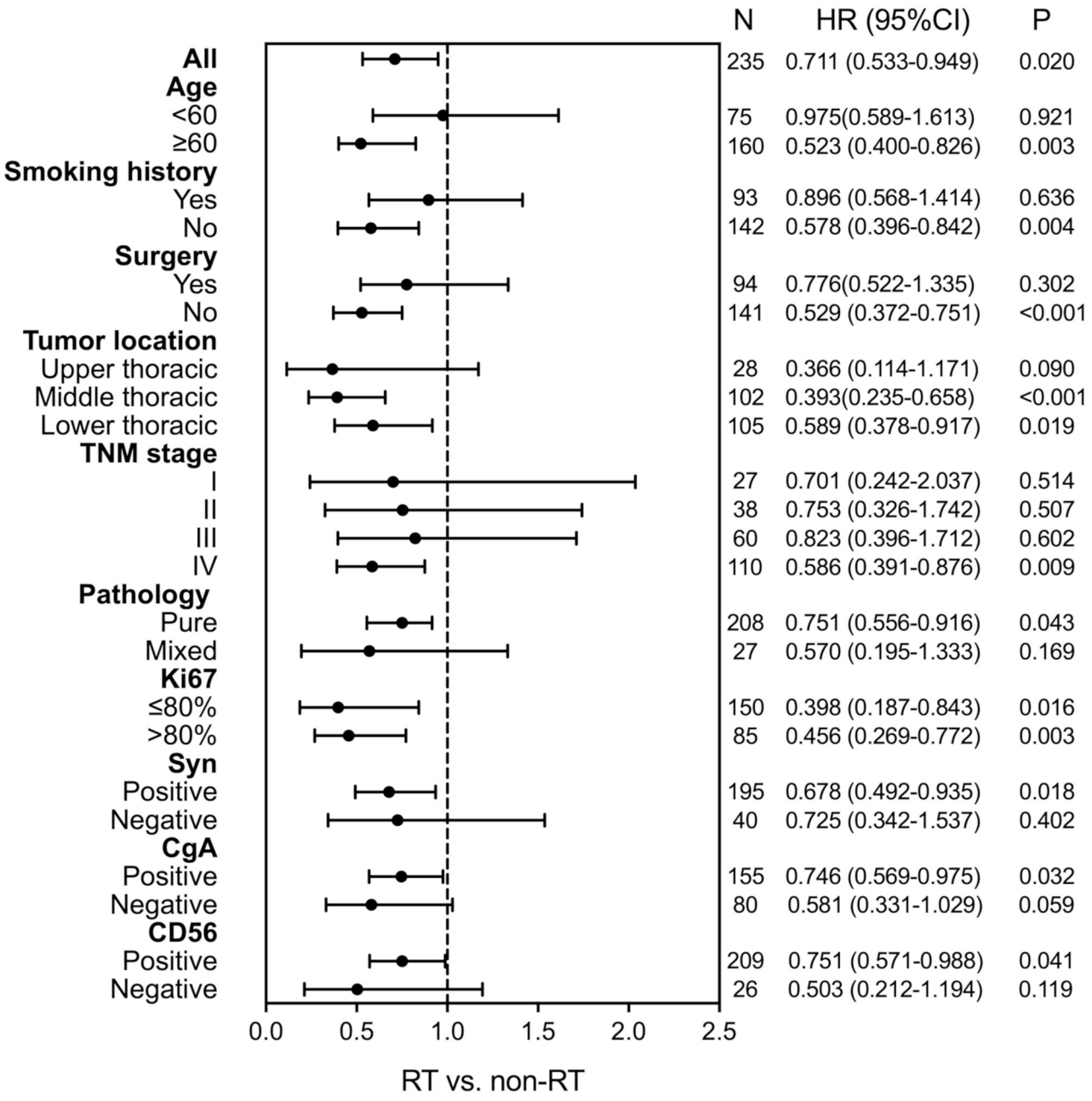

Fig. 3 Multivariate cox regression analysis in different subgroups

SCCE patients should not dismiss RT as a potential treatment option. Subgroup analysis of our study identified that stage IV patients could benefit from RT, with a significant improvement in OS from 10.5 months to 15.3 months (HR: 0.585, 95% CI: 0.415–0.824, $p = 0.002$) compared to patients who did not receive RT. Even in aggressive disease as SCCE, RT still remains an important treatment modality to improve the prognosis of patients.

Recently, the US Food and Drug Administration (FDA) approved atezolizumab (anti-programmed cell death ligand-1 (PD-L1) antibody) as a first-line treatment and nivolumab and pembrolizumab (anti-programmed cell death protein-1 (PD-1) monoclonal antibodies) as third-line monotherapies for patients with SCLC [22–24]. Studies have also showed that immunotherapy may help improve the treatment of SCCE. High levels of tumor-infiltrating lymphocytes (TILs) and a significant subset (40%) exhibited PD-L1 CPS ≥ 1 with preserved human leukocyte antigen (HLA)-class were found in SCCE, suggesting that the PD-1/PD-L1 pathway is a potential therapeutic target for SCCE [25]. The tumor mutation burden (TMB) of SCCE was 3.64 with a predictive objective

response rate of 13.2%, while the PD-L1-positive rate was as high as 43% [26]. Other immune checkpoints such as immune checkpoint B7-H3 (CD276) and lymphocyte-activation gene 3 (LAG-3) were also upregulated, and M2 macrophage infiltration was high in SCCE tumor tissues [26]. PD-L1 expression and CD8 status of TILs were reported to be novel independent prognostic predictors in SCCE (27–28). These observations supported further investigation and application of ICIs in SCCE.

The subgroup analysis of our study showed that patients with stage IV, aged ≥ 60, as non-smokers, with pure histology and neuroendocrine marker (Syn/CgA/CD56) positivity derived significant benefit from RT. For stage IV patients, RT could reduce the tumour burden and alleviates symptoms (e.g., dysphagia, bleeding). In elder patients, the frailty and comorbidities made chemotherapy intolerable, and they may benefit more from RT, which was more tolerable with fewer side effects.

As for the role of smoking, although specific data on SCCE are limited, other researches indicate that smokers always had more side effects, treatment interruptions and poorer outcomes [29–32]. Cigarette smoking increases the concentrations of carboxyhemoglobin in the blood, leading to tissue hypoxia, and impairing tumor oxygenation and normal tissue recovery, thereby reducing efficacy of RT (33–34). Smoking has also been reported to be associated with the risk of radiation pneumonitis and infection in cancer patients [35].

Tumors with strong neuroendocrine features often exhibit high proliferation rates and increased sensitivity to DNA-damaging therapies such as radiotherapy due to impaired DNA repair mechanisms. Compared to pure SCCE, the patients with mixed histology, such as squamous cell carcinoma or adenocarcinoma, may be more heterogeous, less responsive to RT and lead to shorter OS. This finding conflicts with the previous results in other small-cell carcinomas [36–38].

Syn, CgA, and CD56 are markers of neuroendocrine differentiation. Positive expression of these markers indicates neuroendocrine features, a better prognosis (39–40) and may be sensitive to RT [41]. So far, direct correlations between these markers and the efficacy of RT are not well-established.

Our study revealed the important role of RT in improving OS in specific SCCE patients. However, several limitations of our study should be acknowledged. The main shortcomings are the small sample size from a single institution and its retrospective nature. The retrospective nature of the analysis led to some missing data, which may have influenced the prognosis. Meanwhile, there is no consensus on the details of RT, such as the dose, timing, and technology. Although PCI is recommended in SCLC patients who achieve disease control with initial treatment [42], there was no relevant studies in SCCE. In addition, treatment strategies for SCCE and the role of RT may change when RT is combined with immunotherapy. Unfortunately, due to the low incidence of SCCE, the relatively small number of patients in our study did not allow us to answer all the questions. The role of RT and potential efficacy predictors in SCCE still needs to be further investigated with large, multi-center trials.

Conclusion

RT could provide additional benefit to SCCE patients, especially those who do not have surgery. Middle and lower thoracic SCCE patients could both benefit from the addition of RT. RT could improve OS regardless of Ki67 expression level. Subgroup analyses also indicated that stage IV, age ≥ 60, no smoking history, pure SCCE, Syn-positive, CgA-positive, CD56-positive patients could benefit from RT. Further clinical data are required to confirm and extend this conclusion.

Abbreviations

ADC	Adenocarcinoma
AJCC	American Joint Committee on Cancer
CD56	Neuronal cell adhesion molecules
CD276	Immune checkpoint B7-H3
CgA	Chromogranin A
CI	Confidence interval
CRT	Chemoradiotherapy
CT	Chemotherapy
EC	Esophageal carcinoma
ESCC	Esophageal squamous cell carcinoma
FDA	Food and Drug Administration
HLA	Human leukocyte antigen
HR	Hazard ratio
ICIs	Immune-checkpoint inhibitors
LAG-3	Lymphocyte-activation gene 3
NCCN	National Comprehensive Cancer Network
NSE	Neuron-specific enolase
OS	Overall survival
PCI	Prophylactic cranial irradiation
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death ligand-
1PFS	Progression free survival
PSM	Propensity score matching
RCTs	Randomized controlled trials
RT	Radiotherapy
SCC	Squamous cancer cell
S	Surgery
SCCE	Primary small cell carcinoma of the esophagus
SCLC	Small cell lung carcinoma
SEER	Surveillance, Epidemiology, and End Results Program
Syn	Synaptophysin
TILs	Tumor-infiltrating lymphocytes
TMB	Tumor mutation burden
TNM	Tumor, nodes, and metastases
RT	Thoracic radiotherapy

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NA.

Author contributions

HY and HG designed this study and analyzed the data. HY and LY collected and analyzed the data. HY drafted the manuscript and HG revised the manuscript. All authors have read and approved the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the ethics committee of the Affiliated Cancer Hospital of Zhengzhou University. Written informed con- sent was obtained from the patient for this study.

Consent for publication
NA.

Conflict of interest
The authors report no conflicts of interest in this work.

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