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ORIGINAL ARTICLE

Survival outcomes of patients with cervical esophageal cancer who received definitive radiotherapy: a retrospective study conducted in a single institution*

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Abstract

Objective Cervical esophageal cancer (CEC) is a relatively rare condition, with limited treatment options. The current study aimed to assess the survival outcomes of patients with CEC who received definitive radiotherapy.

Methods In total, 63 consecutive patients with CEC who received definitive radiotherapy between 2010 and 2018 were included in this study. The survival outcomes were analyzed based on statistics.

Results The median progression-free survival (PFS) and overall survival (OS) of the patients were 12 and 19 months, respectively. There were no significant differences in terms of survival outcomes between the groups who received radiation doses ≥ 60 and < 60 Gy. Interestingly, in the proximal CEC subgroup, the PFS (P = 0.039), OS (P = 0.031), and loco-regional failure-free survival (LRFFS) (P = 0.005) improved significantly in patients who received a radiation dose ≥ 60 Gy compared with those who received a radiation dose < 60 Gy. However, in the distal CEC subgroup, the PFS, OS, and LRFFS did not significantly improve between patients who received radiation doses ≥ 60 and < 60 Gy. Definitive radiotherapy was well tolerated, and no significant differences were observed in terms of treatment-related toxicities between the groups who received radiation doses ≥ 60 and < 60 Gy.

Conclusion The survival outcomes of patients with CEC should be improved. In proximal CEC, a radiation dose ≥ 60 Gy is significantly correlated with better PFS, OS, and LRFFS. However, further research must be performed to validate this finding.

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Key words: cervical esophageal cancer; definitive radiotherapy; survival outcomes

Cervical esophageal cancer (CEC) is a relatively rare condition, which accounts for 2%–10% of all esophageal carcinomas [1]. Moreover, it is highly prevalent in Eastern Asia and Southern Africa [2]. This condition is defined as a tumor of the esophagus located between the cricoid cartilage and the sternal notch [3]. CEC is commonly diagnosed at a locally advanced stage, and the prognosis is poor, with a 5-year overall survival (OS) rate of 30%–48.3% [4]. Recently, pharyngo-laryngo-esophagectomy is performed for the treatment of such condition. However, the procedure is extensive and it often causes severe complications. Organ-sparing definitive concurrent chemoradiotherapy (dCCRT) is the standard treatment for CEC. Further, it is recommended by the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines [5–6]. Nonetheless, over the past several decades, the survival of patients with CEC has not significantly improved [7].

Due to the low incidence of CEC, studies about this condition are relatively limited. Thus, there is no consensus whether dCCRT can be considered an optimal treatment regimen for CEC. The treatment of CEC is often referred to the esophageal cancer of other sites or hypopharyngeal carcinoma. The randomized phase III INT-0123/RTOG 94-05 trial compared the efficacy of standard-dose radiation (50.4 Gy) versus high-dose radiation (64.8 Gy) for the

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treatment of esophageal cancer. Results showed that dose escalation could not improve local/regional control or survival [8]. However, more than 85% of the patients were diagnosed with adenocarcinoma at various sites of the esophagus. Hence, the results were not applicable to CEC considering that 95% of the cases involved squamous cell carcinoma (SCC). Since the definitive radiotherapy dose for hypopharyngeal carcinoma is up to 70 Gy, some researchers recommend that the standard dose for CEC should be > 50 Gy [9]. Moreover, several studies have reported that a higher local-regional control rate [10–11] and better OS were observed in CEC patients who received a radiation dose > 50.4 Gy [12–13]. However, some studies have contrasting results [14].

To date, an optimal treatment protocol with adequate survival and acceptable toxicity for patients with CEC has not yet been established. To shed light on this issue, the current retrospective study aimed to investigate the survival outcomes of CEC patients who received definitive radiotherapy with different radiation doses.

Patients and methods

Patients

Between January 2010 and March 2018, 63 consecutive CEC patients who received definitive radiotherapy at the Oncology Center of Tongji Hospital, Wuhan, were included in this study. The participants were pathologically diagnosed with SCC. Each patient underwent contrast-enhanced computed tomography (CT) scan or magnetic resonance imaging (MRI) of the cervical spine, chest, abdomen, and brain; bone scan; or ^{18}FDG-positron emission tomography (PET)-CT scan. Cancer staging was performed using the 7th edition of the American Joint Committee on Cancer staging system. The study protocol was approved by the ethics committee of Tongji Hospital.

Treatment details

The patients received intensity-modulated radiotherapy (IMRT) or three-dimensional conformal radiotherapy. Gross tumor volume (GTV) was defined as the volume of the primary tumor and involved lymph nodes based on imaging modalities at diagnosis, including neck/chest CT scan, barium swallow, laryngoscopy, endoscopy/endoscopic ultrasound, and PET-CT scan. The prescription dose for GTV ranged from 50 to 70 Gy for over 5–7 weeks in 25–35 fractions with 5 fractions per week. Clinical tumor volume (CTV) was defined as GTV plus a margin of 3–5 cm longitudinally and 0.7–1 cm radially. The supraclavicular node areas and upper mediastinal areas were also included in the CTV for involved field irradiation (IFI) or elective nodal irradiation (ENI), with a prescription dose of 45–54 Gy. For daily set-up errors in radiation, the planning target volume was defined as CTV plus a margin of 0.5–1.0 cm.

Most patients (n = 42, 66.7%) were treated with concurrent chemoradiotherapy (CCRT). The most common regimen was cisplatin/5-fluorouracil-based chemotherapy (29/42, 69.0%). Meanwhile, the other treatments included oral capecitabine or S1. However, only some patients received radiotherapy due to poor performance or intolerance to chemotherapy.

Follow-up

The median follow-up time was 16 (range: 3–42.0) months. During treatment, the patients were monitored at least once a week to assess for treatment-related toxicities, which were evaluated and scored according to the Common Terminology Criteria for Adverse Events version 4.0. Treatment response was assessed after definitive radiotherapy using imaging modalities, including contrast-enhanced CT scan of the neck and thorax, according to the Response Evaluation Criteria in Solid Tumors version 1.1. After treatment, all patients were followed-up every 3 months within the first 2 years and once every 6 months thereafter. During each follow-up, to evaluate for toxicities and treatment response, the patients underwent physical examination, blood test, and imaging, including CT scan, MRI, ultrasonography, and endoscopy with or without biopsy.

Treatment failure was defined as the persistence or recurrence of the primary lesions or appearance of a new lesion. The failure patterns were identified based on the sites of first failure. Local and regional failure was defined as failure of treatment for the primary tumor or regional lymph nodes. Distant failure was defined as metastasis beyond the primary tumor and regional lymph nodes.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences software version 18.0 (SPSS, Chicago, IL, the USA). The progression-free survival (PFS), loco-regional failure-free survival (LRFFS), distant metastasis-free survival (DMFS), and overall survival (OS) were assessed using the Kaplan–Meier method. Univariate analyses were conducted to identify potential prognostic factors, using $P < 0.10$ as the cutoff value for multivariate analyses. Subsequently, the Cox proportional hazard model was used in the multivariate analyses, and a P value < 0.05 was considered statistically significant. The characteristics and failure pattern were compared between the groups who received high- and standard-dose radiation using the Pearson's chi-square test.

Results

Characteristics of the participants

Most participants (n = 35, 55.5%) presented with stage III disease. Three patients with stage IV disease with bone metastasis at a single site were included, and these patients received definitive radiotherapy. In total, 12 (19.0%) patients presented with hoarseness at diagnosis. Of 63 patients, 56 (88.9%) received IMRT and 7 3DCRT. The median GTV radiation dose was 60 (range: 50–70) Gy in 25–35 fractions. Moreover, 34 (60.7%) and 22 (39.3%) patients received radiations dose ≥ 60 and < 60 Gy, respectively. Of 63 patients, 51 (81.0%) received ENI. The characteristics of the patients are presented in Table 1. No significant difference was observed in terms of characteristics between the groups who received GTV radiation doses ≥ 60 and < 60 Gy (P > 0.05).

Survival analysis and radiation dose

In total, 55 patients died from treatment failure and other non-tumor causes during the follow-up period. The median OS was 19 months; median PFS, 12 months; median LRFFS, 12 months; and median DMFS, 13 months. The survival curves are depicted in Fig. 1.

Based on the Kaplan–Meier analysis using the log-rank test, no significant differences were found in terms of PFS (P = 0.053), OS (P = 0.300), LRFFS (P = 0.193), and DMFS (P = 0.175) between the groups who received radiation doses ≥ 60 Gy and < 60 Gy.

Similar to the effect of radiation dose on PFS, we further divided the patients into the proximal and distal CEC subgroups according to the location of the tumor above or below the middle portion of the cervical esophagus. There were 36 patients in the proximal CEC subgroup and 27 in the distal CEC subgroup. In total, 24 (66.7%) patients in the proximal CEC subgroup and 12 (44.4%) in the distal CEC subgroup received an RT dose ≥ 60 Gy. In the proximal CEC subgroup, six (50%) patients with stage I-II disease and three (25%) without concurrent chemotherapy received an RT dose < 60 Gy. Meanwhile, 11 (45.8%) patients with stage I-II disease and 7 (29.2%) without concurrent chemotherapy received an RT dose ≥ 60 Gy. In the distal CEC subgroup, five (33.3%) patients with stage I-II disease and seven (46.7%) without concurrent chemotherapy received an RT dose < 60 Gy. Meanwhile, three (25.0%) patients with stage I-II and four (33.3%) without concurrent chemotherapy received an RT dose ≥ 60 Gy. Based on the Kaplan–Meier analysis, in the proximal CEC subgroup, a GTV radiation dose ≥ 60 Gy was significantly correlated with better PFS (P = 0.039), LRFFS (P = 0.005), and OS (P = 0.031), but not with DMFS (P= 0.107). The survival curves are presented in Fig. 2. However, in the distal CEV subgroup, the correlation was not significant (PFS, P = 0.131; LRFFS, P = 0.097; DMFS, P = 0.639; and OS, P = 0.132). The GTV and CTV for proximal and distal CEC are depicted in Fig. 3.

Table 1 Patients' characteristics

Characteristics	Radiation dose < 60 Gy (n = 27)	Radiation dose < 60 Gy (n = 36)	P value
Age (years)			0.710
≤ 60	17 (63.0%)	21 (58.3%)	
> 60	10 (37.0%)	15 (41.7%)	
Sex (n, %)			0.127
Male	19 (70.4%)	31 (86.1%)	
Female	8 (29.6%)	5 (13.9%)	
ECOG score			0.710
0–1	17 (63.0%)	21 (58.3%)	
2–3	10 (37.0%)	15 (41.7%)	
T classification (n, %)			0.798
T1–2	6 (22.2%)	9 (25.0%)	
T3–4	21 (77.8%)	27 (75.0%)	
N classification (n, %)			0.369
N0	12 (44.4%)	12 (33.3%)	
N+	15 (55.6%)	24 (66.7%)	
Tumor Location			0.078
Proximal	12 (44.4%)	24 (66.7%)	
Distal	15 (55.6%)	12 (33.3%)	

P < 0.05 was considered to indicate a statistically significant difference. n, number; ECOG, Eastern Cooperative Oncology Group

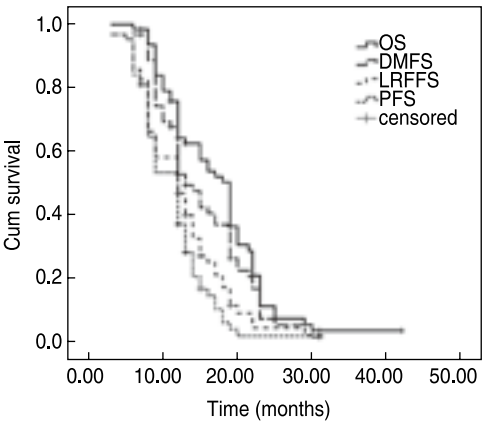

Fig. 1 Survival curves of progression-free survival, loco-regional failure-free survival, distant metastasis-free survival, and overall survival assessed using the Kaplan–Meier method in patients with cervical esophageal cancer

Prognostic factors

A univariate Cox analysis of clinical factors, including gender, age, fistula, neutrophil-to-lymphocyte ratio, hoarseness, T classification, N classification, TNM stage, and GTV radiation dose (cutoff of 60 Gy), was conducted. The results are presented in Table 2. Only hoarseness was significantly associated with worse PFS (P = 0.040), OS (P = 0.008), LRFFS (P = 0.035), and DMFS (P = 0.019).

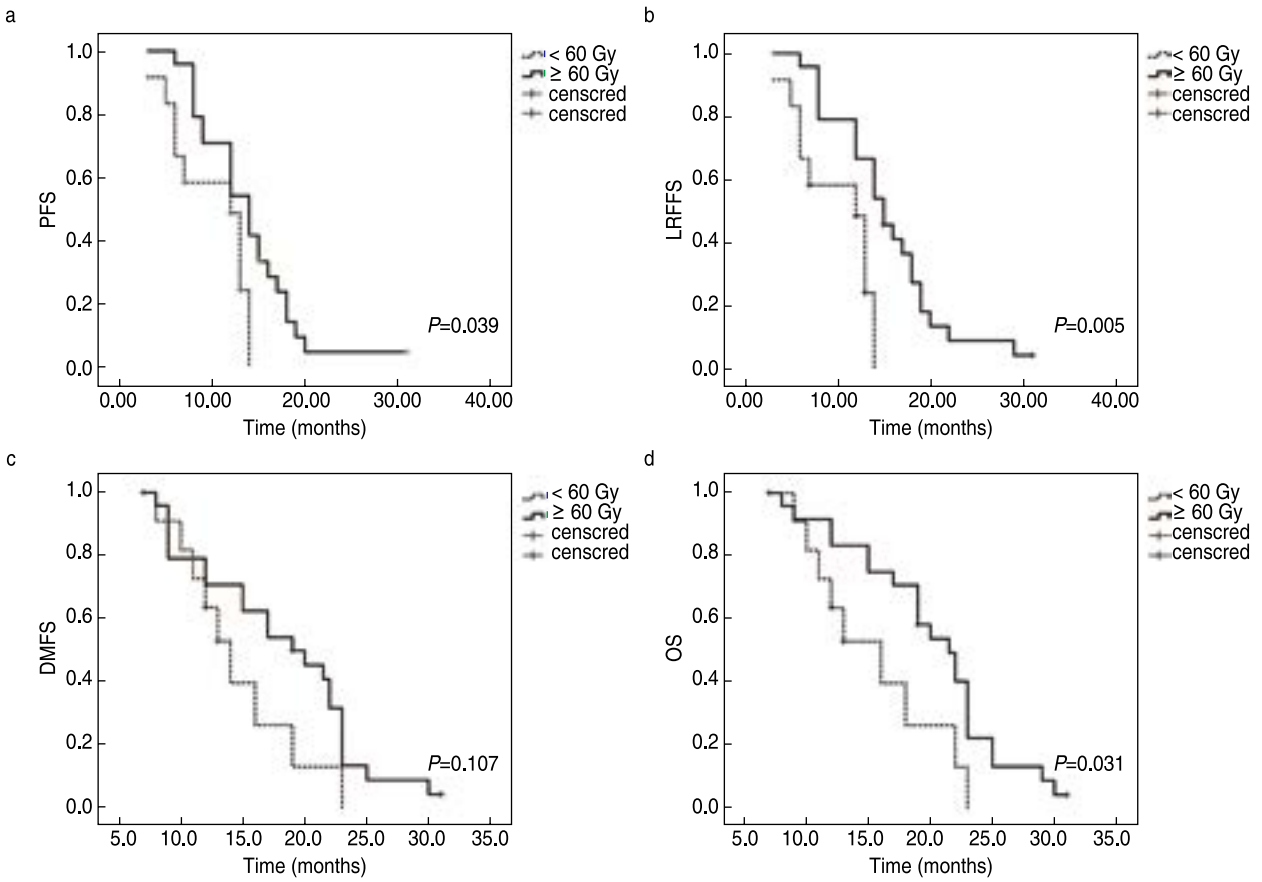

Fig. 2 Survival curves of progression-free survival, loco-regional failure-free survival, distant metastasis-free survival, and overall survival stratified according to radiation dose

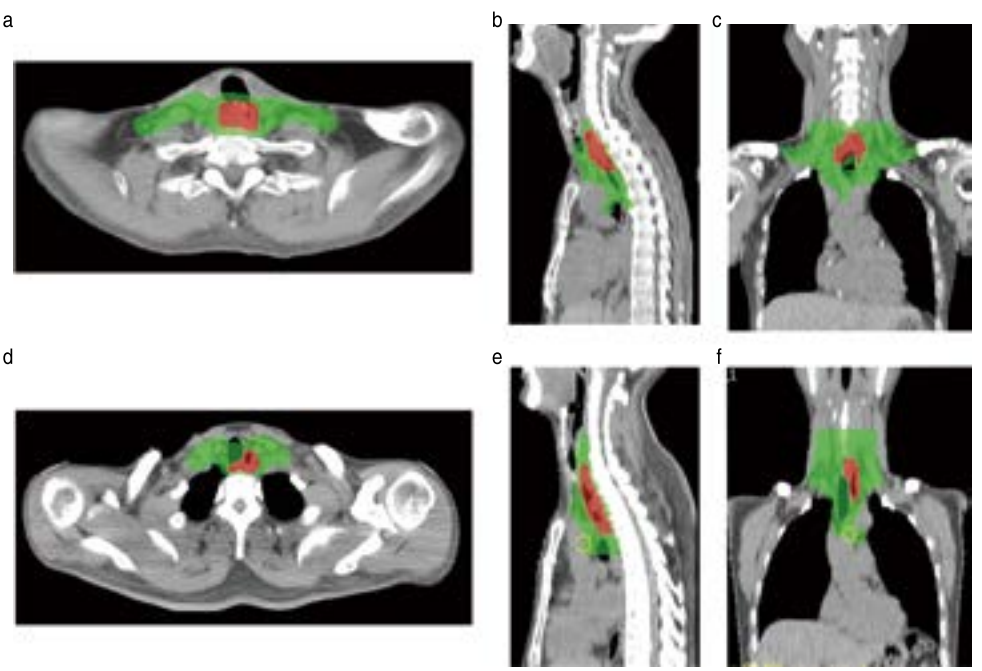

Fig. 3 Gross tumor volume (red area) and clinical tumor volume (green area) for proximal cervical esophageal cancer (CEC) (a–c) and distal CEC (d–f) in patients who received intensity-modulated radiotherapy. a and d, transverse position; b and e, sagittal position; c and f, coronal position

Radiation dose had a slight significant association with poor PFS (P = 0.081). As the cutoff value of the univariate analysis was set to P < 0.01, a multivariate analysis of the association between hoarseness and radiotherapy dose as well as PFS was conducted. Results showed that hoarseness, but not radiation dose, was significantly correlated with PFS (P = 0.040 and 0.115, respectively) (Table 3).

However, in the subgroup analysis, hoarseness was not significantly associated with survival outcome. In the proximal CEC subgroup, four patients presented with hoarseness (PFS, P = 0.341; LRFFS, P = 0.166; DMFS, P = 0.371; and OS, P = 0.229). Meanwhile, in the distal CEC subgroup, eight patients with hoarseness (PFS, P = 0.157; LRFFS, P = 0.097; DMFS, P = 0.055; and OS, P = 0.053).

Treatment failure patterns

In total, 53 patients experienced treatment failure during the follow-up period. Of them, 42 (79.2%) presented with locoregional failure and 14 (22.22%) with distant failure. In patients who received a radiation dose < 60 Gy, 19 (70.37%) developed locoregional failure. Meanwhile, in patients who received a radiation dose ≥ 60 Gy, 23 (63.89%) experienced locoregional failure. The Pearson's chi-square test revealed no significant difference (χ^2 = 0.292; P = 0.589) between the two groups. In the proximal CEC subgroup, 9 (75.0%) and 15 (62.5%) patients who received radiation doses < 60 and ≥ 60 Gy, respectively, developed locoregional failure. However, the result was not significantly different (χ^2 = 0.562; p = 0.453). In the distal CEC subgroup, 11 (73.33%) and 7 (58.33%) patients who received radiation doses < 60 and ≥ 60 Gy, respectively, developed locoregional failure. However, the result was not significantly different (χ^2 = 0.675; P = 0.411).

Toxicities

There were no treatment-related deaths. The most common grade 1 or 2 acute toxicities were mucositis, skin reactions, and hemocytopenia. There was no significant difference in terms of ≥ grade 3 acute toxicities between the groups who received radiation doses < 60 and ≥ 60 Gy (Table 4). In terms of late toxicities, the incidence of esophageal stenosis was similar between the two groups (7.41% *vs* 8.33%, p = 0.893). Moreover, the incidence of tracheoesophageal fistula was higher in the group who received a radiation dose ≥ 60 Gy group than in the group who received a radiation dose < 60 Gy. However, the difference was not significant (13.89% *vs* 7.41%, p = 0.418) (Table 4). Notably, only one patient who received a radiation dose of 70 Gy presented with grade 4 esophageal stenosis.

Discussion

Due to the low incidence of CEC, clinical data on the survival outcomes of definitive radiotherapy are limited. In particular, the number of studies that used modern radiation techniques is extremely low. In the current study, 63 CEC patients, most of whom (56/63, 88.9%) received IMRT, were included. Results showed that there was no significant difference in terms of survival between the groups who received GTV radiation doses ≥ 60 and < 60 Gy. According to the location of the primary tumor above or below the middle portion of the cervical esophagus, the patients were further divided into the proximal and distal CEC subgroups. In the proximal CEC subgroup, the PFS, OS, and LRFFS significantly improved in patients who received a GTV radiation dose ≥ 60 Gy compared with those who received a GTV radiation dose < 60 Gy. Meanwhile, in the distal CEC subgroup, the PFS, OS, and LRFFS did not significantly improve. Univariate and multivariate analyses revealed that hoarseness was the only independent prognostic factor of survival among patients with CEC. No significant difference was observed in terms of the occurrence of severe toxicities.

To date, the largest series, which included 789 CEC

Table 2 Univariate analysis of prognostic factors influencing PFS, OS, LRFFS and DMFS in CEC

Factors	PFS		OS		LRFFS		DMFS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender (Male *vs* Female)	0.793 (0.425-1.481)	0.467	0.663 (0.351-1.251)	0.204	0.585 (0.311-1.102)	0.097	0.872 (0.464-1.639)	0.671
Age (< 60 years *vs* ≥ 60 years)	0.700 (0.408-1.202)	0.196	0.879 (0.509-1.518)	0.644	0.817 (0.477-1.399)	0.461	0.885 (0.517-1.514)	0.655
Fistula	0.790 (0.397-1.571)	0.502	0.753 (0.377-1.504)	0.422	0.587 (0.293-1.176)	0.133	0.901 (0.453-1.791)	0.765
NLR (< 4 *vs* ≥ 4)	0.795 (0.417-1.515)	0.485	0.928 (0.478-1.803)	0.825	0.862 (0.453-1.639)	0.650	0.806 (0.425-1.530)	0.510
Hoarseness	0.506 (0.264-0.968)	0.040	0.398 (0.202-0.786)	0.008	0.503 (0.265-0.953)	0.035	0.452 (0.232-0.879)	0.019
T classifi-cation (T1-2 *vs* T3-4)	0.793 (0.417-1.506)	0.478	0.876 (0.460-1.668)	0.686	0.672 (0.353-1.279)	0.226	0.981 (0.516-1.864)	0.952
N classifi-cation (N0 *vs* N+)	0.739 (0.426-1.281)	0.281	0.710 (0.404-1.247)	0.233	0.751 (0.427-1.318)	0.318	0.754 (0.435-1.307)	0.314
TNM stage (1-2 *vs* 3-4)	0.873 (0.507-1.503)	0.624	0.751 (0.430-1.312)	0.314	0.837 (0.479-1.462)	0.532	0.808 (0.470-1.390)	0.442
RT Dose (< 60 Gy *vs* ≥ 60 Gy)	1.643 (0.941-2.869)	0.081	1.310 (0.758-2.265)	0.334	1.396 (0.813-2.398)	0.227	1.401 (0.822-2.388)	0.216

P < 0.05 was considered to indicate a statistically significant difference. PFS, progression free survival; OS, overall survival; LRFFS, loco-regional failure-free survival; DMFS, distance metastasis free survival; CEC, cervical esophageal carcinoma; HR, hazard ratio; CI, confidence interval; NLR, neutrophil to lymphocyte ratio; RT, radiotherapy

Table 3 Multivariate analysis of prognostic factors influencing PFS in CEC

Endpoint	Variable	HR	95% CI	*P* value
PFS	Hoarseness	0.506	0.264-0.968	0.040
	RT Dose	1.561	0.893-2.731	0.115

P < 0.05 was considered to indicate a statistically significant difference. PFS, progression free survival; CEC, cervical esophageal carcinoma; RT, radiotherapy; HR, hazard ratio; CI, confidence interval

Table 4 Toxicities ≥ grade 3 in CEC patients received definitive radiotherapy stratified by radiation dose

Toxicities ≥ Grade 3	Dose < 60 Gy *n* = 27	Dose ≥ 60 Gy *n* = 36	*P* value
Acute toxicity			
Dysphagia	2 (7.41%)	4 (11.11%)	0.620
Skin	0 (0%)	1 (2.78%)	0.383
Mucositis	2 (7.41%)	1 (2.78%)	0.393
Hemocytopenia	1 (3.70%)	2 (5.56%)	0.733
Chronic Dysphagia			
Esophageal stenosis	2 (7.41%)	3 (8.33%)	0.893
Tracheoesophageal fistula	2 (7.41%)	5 (13.89%)	0.418

P < 0.05 was considered to indicate a statistically significant difference. CEC, cervical esophageal carcinoma

patients from the National Cancer Data Base (NCDB), reported that compared with standard-dose radiation (50–50.4 Gy), medium-dose (50.4–66 Gy) or high-dose (66–74 Gy) radiation could not significantly improve OS [14]. This result was consistent with that of the INT-0123/RTOG 94-05 trial8 and other studies [15]. However, there are still controversies regarding this finding. Even in the NCDB analysis, from 2004 to 2013, 73% of CEC patients were treated with radiation doses > 50.4 Gy, indicating that most oncologists support dose escalation for CEC. One prospective clinical trial on CEC in Japan, which included 30 patients, used radiation therapy with 3D CRT at a dose of 60 Gy in 30 fractions [16]. Recently, Herrmann *et al* reported that high-dose (> 56 Gy) radiation was significantly correlated with better DFS and OS in proximal esophageal carcinoma. Moreover, Wang *et al* showed that a radiation dose > 50 Gy significantly increased the rate of complete response and OS in patients with cervical and upper thoracic esophageal cancer from the MD Anderson Cancer Center [12]. A study in Canada conducted a retrospective analysis of 81 CEC patients who received consecutive treatment based on three protocols (protocol 1: two-dimensional radiation (2D RT) of 54 Gy in 20 fractions with 5-Fu plus mitomycin C/cisplatin; protocol 2: 3D CRT ≥ 60 Gy in 30 fractions with ENI plus cisplatin; and protocol 3: IMRT ≥ 60 Gy in 30 fractions with ENI plus cisplatin). Results showed that the patients treated with protocol 3 had better OS than those treated with protocol 1, with benefits similar to those of protocol 2 [17].

The contrasting results are partly attributed to the use of different radiation techniques. In the RTOG 94-05 trial, 2D RT was used, which increased the incidence of radiation toxicities in normal tissues when the dose reached 64.8 Gy. Only 67% of patients completed the radiation therapy in the group who received a dose of 64.8 Gy and 83% in the group who received a dose of 50.4 Gy. Moreover, there were 11 treatment-related deaths in the high dose arm and 2 in the 50.4 Gy arm, which was one of the main causes of treatment failure. Therefore, high-dose radiation using old techniques results in severe side effects, which might compromise the benefit of high-dose therapy on tumors. However, the modern photon-based radiotherapy techniques, such as 3D CRT, IMRT and volumetric-modulated arc therapy, can have high conformity to the target volume, which concurrently facilitates the delivery of higher doses to tumors and the sparing of adjacent normal organs at risk. Retrospective studies showed that IMRT could improve local-regional control and OS among CEC patients [17–18]. Thus, more data about the efficacy of high-dose radiation using modern techniques in CEC must be collected to help direct clinical treatment.

In the current study, of 63 patients, 34 (60.7%) and 22 (39.3%) received radiation doses ≥ 60 Gy and < 60 Gy, respectively. Moreover, 56 (88.9%) patients received IMRT and seven 3D CRT. However, high-dose radiation did not significantly improve survival compared with standard-dose radiation. However, a similar trend was observed for PFS ($P = 0.053$). The biological behaviors of tumor usually differ due to location, such as left and right side of the colon. Hence, we further divided the patients into the proximal and distal CEC subgroups according to the location of the primary tumor above or below the middle portion of the cervical esophagus. Notably, in the proximal CEC subgroup, high-dose radiation was significantly correlated with better PFS, LRFFS, and OS. Meanwhile, the difference was not significant in the distal CEC subgroup. Results showed that proximal CEC might be more analogous to hypopharyngeal carcinoma, and high-dose radiation (≥ 60 Gy) could improve the prognosis of patients. However, distal CEC might be more analogous to thoracic esophageal carcinoma. Kim *et al* reported that compared with the thoracic esophagus, the cervical esophagus could receive high-dose radiation because only a small portion of the lungs is irradiated during radiotherapy [11]. Similar with this standpoint, the proximal CEC subgroup in our study could tolerate a higher radiation dose compared with the distal CEC subgroup, as the primary tumor is mainly located in the cervical esophagus with less extension to the thoracic esophagus. Thus, high-dose radiation is more advantageous in proximal CEC than in distal CEC.

Considering an abundant lymphatic drainage,

metastasis to regional lymph nodes is common in CEC. However, the delineation of CTV, mainly regarding the need for ENI, still remains controversial. Hirano *et al* reported that in hypopharyngeal carcinoma and CEC, the incidence rates of cervical (levels II–IV) and upper mediastinal lymph nodal metastasis were 85.7% and 33.3%, respectively [19]. Moreover, 0% to 25% patients treated with dCCRT or dRT developed regional lymph node recurrence with ENI versus at least 25% without ENI [20–22]. The NCCN guidelines recommend that prophylactic radiation of cervical and supraclavicular nodes should be considered particularly if the nodal classification is N1 or greater [5]. Conversely, some studies do not recommend ENI because a wide radiation field might aggregate toxicity and interrupt or even terminate dCCRT and does not improve survival [4, 23]. A recent study showed that ENI might destruct lymphocytes in the nearby lymph nodes and affect immune response due to radiation, which were critical for tumor control [24] In our study, 51 (81.0%) of 63 patients, including 12 patients with N negative, received ENI according to the physician's discretion.

In previous studies, CEC patients received definitive radiotherapy, and the 3-year OS rate ranged from less than 35% to nearly 40% [7, 13, 25]. However, in this study, the median OS was only 19 months, which is relatively poor. One of the main causes of this outcome was advanced disease stage. That is, 48 (76.2%) patients with stage T3–4 disease, 35 (55.5%) with stage III disease, and 3 with stage IV disease with bone metastasis at a stable single site. These patients could also benefit from definitive radiotherapy. Another reason is that 33.3% of patients were treated without concurrent chemotherapy due to poor performance or intolerance to CCRT, which might reduce disease control and survival.

An analysis revealed that locoregional failure was still the main pattern of failure in CEC patients. Moreover, even in proximal CEC, the difference in locoregional control rate was not significant between the groups who received GTV radiation doses ≥ 60 Gy and < 60 Gy. This result indicated that high-dose radiation (≥ 60 Gy) might only delay, but not prevent, the occurrence of locoregional failure.

In addition, hoarseness, which is caused by tumor invasion or compression of the recurrent laryngeal nerve, was considered an independent prognostic factor of survival in patients with CEC. However, in a subgroup analysis (proximal and distal CEC subgroups), hoarseness did not significantly affect survival outcomes, which might be attributed to the limited number of patients included in the study. Moreover, other studies showed the prognostic role of hoarseness in CEC [25], which must be considered in clinical settings.

The current study had several limitations due its retrospective nature. First, 63 patients were included in the study, which is relatively small. Moreover, the data used were from a single institution, and this might have affected the reliability of the findings. Second, potential confounding factors, including different characteristics (such as clinical stage, concurrent chemotherapy, and ununiform chemotherapy regimens), might also limit the applicability of the conclusion. However, since CEC is a rare disease, large-scale prospective multicenter randomized control trials are challenging to perform. Thus, retrospective studies are essential in obtaining evidence for clinical treatment.

In conclusion, for proximal CEC, a GTV radiation dose ≥ 60 Gy was significantly correlated with better PFS, OS, and LRFFS. Moreover, the survival of patients with whole and distal CEC did not significantly improve. However, the treatment-related toxicities were acceptable. Proximal and distal CEC might have distinct biological behaviors, which are important in the selection of clinical treatment. Proximal CEC was more analogous than hypopharyngeal carcinoma, and patients with this condition could benefit from high-dose radiation (≥ 60 Gy). Meanwhile, distal CEC was more analogous than thoracic esophageal carcinoma. Thus, high-dose radiation was not beneficial for patients with distal CEC. Further prospective randomized controlled clinical trials must be conducted to validate the results of the current study. Considering the opportunities and challenges of radiotherapy [26], in the future, optimal CCRT regimens, radiosensitizing agents, and new therapeutic targets must be developed to improve the survival outcomes of CEC patients.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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