Outcomes and prognostic factors for patients with cervical esophageal cancer undergoing definitive radiotherapy or chemoradiotherapy

Xin-xin Du[1,2,3#], Rong Yu[1#], Zhen-fei Wang[1,4#], De-cheng Du[1], Qiao-yun Liu[1], Run-mei Wang[1], Shi-rong Kang[5*], Hao Yang[1*]

[1]Department of Radiotherapy, Inner Mongolia Cancer Hospital, The Affiliated People's Hospital of Inner Mongolia Medical University, Hohhot, China, [2]Department of Obstetrics and Gynecology, Chinese PLA General Hospital, Beijing, China, [3]Research Group for Reproductive Medicine and IVF-Laboratory, Department of Obstetrics and Genecology, University of Cologne, Cologne, Germany, [4]Tumor Molecular Diagnostic Laboratory, Inner Mongolia Cancer Hospital, The Affiliated People's Hospital of Inner Mongolia Medical University, Hohhot, China, [5]Department of Thoracic Surgery, The Affiliated People's Hospital of Inner Mongolia Medical University, Hohhot, China

ABSTRACT

Cervical esophageal cancer (CEC) is uncommon, accounting for less than 5% of all esophageal cancers. The management of CEC is controversial. This study investigated treatment outcomes and prognostic factors of survival in CEC patients undergoing definitive radiotherapy or concurrent chemoradiotherapy (CCRT). Ninety-one CEC patients were treated by intensity-modulated radiation therapy (IMRT) and three-dimensional conformal radiation therapy (3DCRT) between July 2007 and September 2017. The mean prescription dose was 64 Gy (range 54–70 Gy) delivered as 1.8–2.2 Gy per fraction per day, 5 days a week. Out of 91 patients, 34 received concurrent cisplatin-based chemotherapy (CT) including 18 patients who also received neoadjuvant CT. Overall survival (OS), locoregional failure-free survival (LRFFS), and progression-free survival (PFS) were estimated by the Kaplan–Meier method. Prognostic factors of survival were determined in univariate (log-rank test) and multivariate (Cox proportional hazard model) analysis. Treatment-related toxicity was also assessed. Median follow-up time for all patients was 19 months. Two-year OS, LRFFS and PFS of all patients were 58.2%, 52.5% and 48.1%, respectively. Clinical stage was an independent prognostic factor for OS (HR = 2.35, 95% CI: 1.03–5.37, $p = 0.042$), LRFFS (HR = 3.84, 95% CI: 1.38–10.69, $p = 0.011$), and PFS (HR = 2.68, 95% CI: 1.11–6.45, $p = 0.028$). Hoarseness was an independent prognostic factor for OS (HR = 2.10, 95% CI: 1.05–4.19, $p = 0.036$). CCRT was independently associated with better LRFFS (HR = 0.33, 95% CI: 0.14–0.79, $p = 0.012$). 3DCRT and IMRT with concurrent CT is well-tolerated and may improve local tumor control in CEC patients. Advanced clinical stage and hoarseness are adverse prognostic factors for OS, LRFFS, and PFS in CEC.

KEY WORDS: Cervical esophageal carcinoma; radiotherapy; chemoradiotherapy; prognosis; disease management; survival; 3DCRT; IMRT; concurrent chemoradiotherapy

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INTRODUCTION

Cervical esophageal cancer (CEC) is relatively uncommon, accounting for less than 5% of all esophageal cancers [1]. The management of CEC is controversial due to the low incidence and a lack of studies investigating specifically treatment strategies and outcomes in CEC. In most available studies, CEC is analyzed together with carcinomas of the hypopharynx and thoracic esophagus, even though it is anatomically distinct from both [2,3]. Treatment modalities for CEC include surgical resection with or without neoadjuvant chemoradiotherapy (CRT) and definitive radiotherapy (RT) with or without concurrent chemotherapy (CT) [4-6].

Minimally invasive surgical approaches that preserve organ shape and function were the treatment of choice for CEC, however, the risk of complications and morbidity and mortality rates associated with surgical resection of CEC remain high. RT, on the other hand, has a major positive impact on the quality of life (QOL) of patients with CEC, since it allows the preservation of both the larynx and esophagus [7]. Therefore, RT has become the preferred treatment for CEC in recent years. Moreover, randomized trials on esophageal cancer [8]

*Corresponding authors: Hao Yang and Shi-rong Kang, Inner Mongolia Cancer Hospital, Zhaowuda Road, Hohhot 010020, Inner Mongolia, P.R. China. Phone: 00-86-0471-3280846; Fax: 00-86-0471-3280846.
E-mail: haoyang050201@163.com (Hao Yang)
793989879@qq.com (Shi-rong Kang)
#These authors equally contributed.

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and squamous cell head and neck cancer [9,10] showed that neoadjuvant chemotherapy (NAC) and concurrent CRT (CCRT) improve the locoregional tumor control and organ preservation in patients.

Technological advances led to the development of improved radiation delivery techniques such as intensity-modulated radiation therapy (IMRT) and its novel form volumetric-modulated arc therapy (VMAT), which have several advantages in cancer treatment over three-dimensional conformal radiation therapy (3DCRT). Studies comparing the efficacy of 3DCRT and IMRT in the treatment of esophageal cancer show that IMRT provides improved planning target volume coverage and dose conformity as well as a reduced dose to adjacent normal tissues [11-15].

In the current study, we investigated treatment outcomes and prognostic factors of survival in CEC patients undergoing definitive RT or CCRT, with the overall goal to help guide decision making for treatment of CEC.

MATERIALS AND METHODS

Patients

A total of 91 patients met the following inclusion criteria: 1) pathological confirmation of cervical esophageal squamous cell carcinoma (CESCC); 2) permission with upper mediastinal lymph node metastasis (M1 lymph node/stage IV esophageal cancer), with no evidence of other distant metastases; 3) completed RT with/without CT; 4) Karnofsky Performance Status (KPS) score ≥70; and 5) age of 75 years or younger. All patients underwent definitive RT or CCRT at our institution from July 2008 to June 2015. Prior to RT, a detailed medical history was obtained from patients and physical examination, barium-swallow X-ray examination, a computed tomography (CT) scan of the neck, chest and abdomen, bronchoscopy, endoscopic ultrasound of the esophagus, and 18F-fluorodeoxyglucose-positron emission tomography (18F-FDG PET) were performed. Tumors were staged according to the 6th edition of the American Joint Committee on Cancer (AJCC) staging system for esophageal cancer.

Radiotherapy

3DCRT and IMRT, optimized using the Pinnacle treatment planning system (Pinnacle3 version 9.6, Philips Medical Systems, Andover, MA), were applied to all patients. Treatments were delivered using a linear accelerator with dynamic multileaf collimator system (6 MV photon beams) and multiple field technique.

The gross tumor volume (GTV) included the primary tumor and involved regional lymph nodes, determined by multiple imaging examinations. The clinical target volume (CTV) was defined as GTV and additional 0.8–1.0-cm margins in the radial direction and 3-cm margins in the cranial-caudal direction from the GTV. Elective nodal irradiation, including the area drained by adjacent involved lymph nodes, bilateral levels II–IV of the cervical lymph node area, supraclavicular fossa, and upper mediastinal of the lymph node area [16]. The planning target volume (PTV) included the CTV plus a 0.5-cm margin. The organs at risk (OARs) were contoured and comprised the larynx, parotid gland, thyroid gland, trachea, spinal cord, lungs, and heart.

The prescribed dose was 54–70 Gy for 95% GTV delivered as 1.8–2.2 Gy per fraction, once per day, five days per week. The prophylactic dose was 50–54 Gy for 95% CTV. The doses received by OARs were constrained as follows: lungs V20 <30 %, V30 <20%; heart V30 <40%, V40 <30%; and a maximum dose for the spinal cord of <45 Gy.

Chemotherapy

Out of 91 patients treated with RT, 18 patients (19.8%) also received NAC consisting of two cycles of intravenous cisplatin (75 mg/m^2) and 5-fluorouracil (5-FU, 1000 mg/m^2/day) administered as continuous 24-hour infusion for four days every three weeks. A total of 34 patients (37.4%) received CCRT consisting of cisplatin alone (40 mg/m^2) every week, cisplatin/5-FU or cisplatin (75 mg/m^2)/paclitaxel (60 mg/m^2) every three weeks. The remaining 57 patients (62.6%) received RT alone due to concerns about adverse effect or intolerance to CCRT.

Patient follow-up

Patients were followed up one month after treatment completion, every three months during the first two years, every six months for three to five years, and annually after five years. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0. Evaluation tools included imaging techniques and biopsy when tumor recurrence was suspected.

Statistics

Statistical analyses were performed using SPSS for Windows, Version 13.0. (SPSS Inc., Chicago, IL, USA). The endpoints were overall survival (OS), locoregional failure-free survival (LRFFS) and progression-free survival (PFS). Each endpoint was calculated from the date of initial diagnosis by biopsy. LRF was defined as local tumor persistence/recurrence, regional lymph node persistence/recurrence, or death. OS, LRFFS and PFS was defined as the time from initial diagnosis to death from any cause or last follow-up, locoregional tumor persistence/recurrence and evidence of tumor progression, respectively. Locoregional

recurrence was defined as recurrence at the primary site or regional lymph nodes. Survival data were analyzed using the Kaplan–Meier method and log-rank test. Univariate analysis of prognostic factors of OS, LRFFS and PFS was performed using the log-rank test and multivariate analysis was carried out using the Cox proportional hazards model. Two-sided tests were used and p <0.05 was considered statistically significant.

RESULTS

Patients

A total of 91 patients with CEC who were treated with RT were included in the study. Thirty-four patients (37.4%) received concurrent cisplatin-based CT, including 18 patients who also received NAC. Fifty-seven patients (62.6%) were treated with RT alone. Table 1 summarizes clinicopathological characteristics and treatment of CEC patients.

Acute and late treatment-related toxicities

Among 91 CEC patients, the most frequently observed acute toxicities were grade 1 and 2. Common grade 1 and 2 acute toxicities were mucositis and esophagitis, observed in 20 (22%) and 22 (24.2%) cases, respectively. Nine patients (10%) experienced grade 3 acute hematologic toxicity. Three patients (3.3%, all three treated with CCRT only) developed grade 3 acute gastrointestinal toxicity. Dysphagia was the most common late toxicity, and six patients (6.6%) experienced severe dysphagia requiring intervention. Other late toxicities were grade 1 radiation pneumonitis and radiation-induced brachial plexus injury.

Survival

The median follow-up time for all patients was 19 months. The two-year OS, LRFFS and PFS for all patients were 58.2%, 52.5% and 48.1%, respectively (Figure 1).

Prognostic factors

Table 2 shows prognostic factors of survival in CEC according to the univariate analysis. Hoarseness, advanced clinical stage (III-IV), tumor length (>5 cm), GTV volume (≥45 cc) and treatment time (>42 days) were significant prognostic factors for poor OS, LRFFS and PFS. GTV dose (<66 Gy), number of fractions (>30 fractions), and 3DCRT technique had an adverse effect on OS. Weight loss (≥10%), distant metastasis (nonregional lymph nodes) and non-CCRT were associated with a worse LRFFS. Lymph node metastasis (N1) was associated with a worse PFS (Figure 2).

TABLE 1. Demographic and clinicopathological characteristics of patients

Characteristics	Category	Number of patients (%)
Mean age (SD)		61.7 (10.9)
Gender	Male	62 (68.1)
	Female	29 (31.9)
Weight loss	≥10%	31 (34.1)
	<10%	60 (65.9)
KPS	70-90	75 (82.4)
	≥90	16 (17.6)
Hoarseness	Yes	19 (20.9)
	No	71 (79.1)
T stage	T1-2	41 (45.0)
	T3	40 (44.0)
	T4	10 (11.0)
N stage	N0	41 (45.0)
	N1	50 (55.0)
M stage	M0	83 (91.2)
	M1	8 (8.8)
Overall stage	I-II	52 (57.1)
	III-IV	39 (42.9)
Pathological grade	G1	27 (29.7)
	G2	46 (50.5)
	G3	18 (19.8)
Tumor extension	CE	31 (34.1)
	CE+HP	9 (9.9)
	CE+TE	51 (56.0)
Tumor length	≤5 cm	56 (61.5)
	>5 cm	35 (38.5)
Multiple primary carcinoma	Yes	10 (11.0)
	No	81 (89.0)
GTV volume	<45 cc	50 (54.9)
	≥45 cc	41 (45.1)
CCRT	Yes	34 (37.4)
	No	57 (62.6)
NAC	Yes	18 (19.8)
	No	73 (80.2)
Radiotherapy technique	3DCRT	27 (29.7)
	IMRT	64 (70.3)
Number of fractions	≤30 fractions	59 (64.8)
	>30 fractions	32 (35.2)
GTV dose	<66 Gy	43 (47.3)
	≥66 Gy	48 (52.7)
Treatment time	≤42 days	40 (44.0)
	>42 days	51 (56.0)

KPS: Karnofsky performance status; CE: Cervical esophagus; HP: Hypopharyngeal extension; TE: Thoracic esophageal extension; CCRT: Concurrent chemoradiotherapy; NAC: Neoadjuvant chemotherapy; GTV: Gross tumor volume; 3DCRT: Three-dimensional conformal radiation therapy; IMRT: Intensity-modulated radiation therapy; TNM: Tumor-node-metastasis

Table 3 summarizes the multivariate analysis results. Hoarseness (HR = 2.10, 95% CI: 1.05–4.19, p = 0.036) and clinical stage III-IV (HR = 2.35, 95% CI: 1.03–5.37, p = 0.042) were independent prognostic factors of OS. Clinical stage III-IV was also an independent factor of LRFFS (HR = 3.84, 95% CI: 1.38–10.69, p = 0.011) and PFS (HR = 2.68, 95% CI: 1.11–6.45, p = 0.028). CCRT was independently associated with a better LRFFS (HR = 0.33, 95% CI: 0.14–0.79, p = 0.012).

TABLE 2. Univariate analysis of two-year OS, LRFFS and PFS in CEC patients

Characteristics	OS			LRFFS			PFS		
	%	χ^2	*p*	%	χ^2	*p*	%	χ^2	*p*
Age (years)									
≤60	51.0	2.417	0.120	62.1	0.084	0.773	44.6	2.481	0.115
>60	60.2			59.0			61.6		
Gender									
Male	48.8	3.850	0.050	56.8	0.100	0.752	52.6	0.097	0.755
Female	70.8			64.3			47.4		
Weight loss									
<10%	65.2	2.689	0.101	70.6	7.574	0.006	66.2	3.479	0.062
≥10%	43.8			43.3			37.2		
KPS									
≥90	63.8	0.085	0.771	65.9	2.393	0.122	59.4	3.221	0.073
70-90	55.6			54.8			44.1		
Hoarseness									
No	68.1	8.379	0.004	75.3	12.055	0.001	59.9	7.388	0.007
Yes	38.8			43.6			36.9		
T stage									
T1-2	68.2	1.894	0.169	57.1	0.921	0.337	56.0	2.318	0.128
T3	52.5			56.0			53.3		
T4	52.0			51.1			42.9		
N stage									
N0	63.2	3.659	0.056	71.4	3.294	0.070	66.1	4.427	0.035
N1	60.9			45.9			39.9		
M stage									
M0	58.6	0.001	0.981	64.1	5.544	0.019	51.9	7.010	0.008
M1	56.0			39.9			30.0		
Overall stage									
I-II	71.4	13.539	0.000	76.5	12.948	0.000	72.0	14.963	0.000
III-IV	40.0			36.6			32.9		
Pathological grade									
G1	53.0	0.448	0.503	64.0	0.131	0.717	60.1	0.893	0.345
G2	52.7			50.6			56.8		
G3	56.8			64.8			50.2		
Tumor extension									
CE	65.4	0.921	0.337	76.0	1.475	0.225	59.9	0.015	0.904
CE+HP	60.0			60.0			40.0		
CE+TE	49.8			61.0			44.5		
Tumor length									
≤5 cm	70.9	19.293	0.000	73.3	12.868	0.000	69.6	11.774	0.000
>5 cm	43.6			34.5			34.1		
Multiple primary carcinoma									
No	73.1	0.371	0.542	59.9	0.002	0.963	56.6	0.227	0.634
Yes	66.7			63.5			63.5		
GTV volume									
<45 cc	67.1	13.370	0.000	69.0	8.366	0.004	68.5	8.412	0.004
≥45 cc	44.2			48.2			32.4		
CCRT									
Yes	64.6	2.652	0.103	71.0	3.885	0.049	62.8	1.991	0.158
No	55.0			53.1			53.1		
NAC									
Yes	66.5	1.838	0.175	64.2	0.755	0.385	58.8	0.497	0.481
No	55.8			59.1			50.5		
Radiotherapy technique									
3DCRT	42.0	5.165	0.023	55.0	0.422	0.516	48.8	0.099	0.753
IMRT	76.8			67.9			53.7		
Number of fractions									
≤30 fractions	65.7	4.184	0.041	70.7	0.057	0.811	54.5	0.076	0.738
>30 fractions	44.7			56.5			46.6		

(Contd...)

TABLE 2. *(Continued)*

GTV dose									
<66 Gy	54.0	4.014	0.045	59.2	0.142	0.706	50.3	0.117	0.732
≥66 Gy	62.2			59.9			54.2		
Treatment time									
≤42 days	87.5	15.114	0.000	87.5	9.759	0.002	65.4	7.456	0.006
>42 days	41.0			41.5			35.6		

CEC: Cervical esophageal cancer; KPS: Karnofsky performance status; CE: Cervical esophagus; HP: Hypopharyngeal extension; TE: Thoracic esophageal extension; CCRT: Concurrent chemoradiotherapy; NAC: Neoadjuvant chemotherapy; GTV: Gross tumor volume; 3DCRT: Three-dimensional conformal radiation therapy; IMRT: Intensity-modulated radiation therapy; OS: Overall survival; LRFFS: Locoregional failure-free survival; PFS: Progression-free survival; TNM: Tumor-node-metastasis

TABLE 3. Multivariate analysis of two-year OS, LRFFS and PFS in CEC patients

Characteristics	OS	*P*	LRFFS	*P*	PFS	*P*
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
Weight loss						
≥10% vs. <10%	1.09 (0.53–2.23)	0.811	1.70 (0.77–3.76)	0.191	1.21 (0.58–2.52)	0.609
Hoarseness						
Yes vs. No	2.10 (1.05–4.19)	0.036	2.03 (0.96–4.30)	0.063	1.67 (0.85–3.29)	0.136
N stage						
N0 vs. N1	0.71 (0.29–1.75)	0.462	0.75 (0.29–1.96)	0.555	0.79 (0.35–1.77)	0.563
M stage						
M0 vs. M1	0.52 (0.16–1.73)	0.288	1.11 (0.41–3.04)	0.836	1.58 (0.62–4.02)	0.333
Overall stage						
III-IV vs. I-II	2.35 (1.03–5.37)	0.042	3.84 (1.38–10.69)	0.011	2.68 (1.11–6.45)	0.028
Tumor length						
>5 cm vs. ≤5 cm	1.91 (0.50–7.22)	0.343	1.50 (0.37–6.05)	0.570	2.51 (0.68–9.29)	0.170
GTV volume						
≥45 cc vs. <45 cc	1.26 (0.34–4.67)	0.732	0.86 (0.22–3.37)	0.830	0.68 (1.90–2.42)	0.548
CCRT						
Yes vs. No	0.65 (0.31–1.35)	0.246	0.33 (0.14–0.79)	0.012	0.53 (0.26–1.10)	0.086
Radiotherapy technique						
3DCRT vs. IMRT	0.74 (0.35–1.58)	0.435	1.91 (0.84–4.33)	0.124	1.63 (0.75–3.56)	0.219
Number of fractions						
≤30 vs. >30 fractions	0.95 (0.44–2.03)	0.886	0.57 (0.25–1.31)	0.186	0.86 (0.41–1.83)	0.699
GTV dose						
<66 Gy vs. ≥66 Gy	1.34 (0.67–2.69)	0.409	1.16 (0.58–2.35)	0.672	1.14 (0.61–2.15)	0.678
Treatment time						
>42 days vs. ≤42 days	1.82 (0.92–3.59)	0.086	1.86 (0.934–3.72)	0.078	1.71 (0.74–3.99)	0.211

CEC: Cervical esophageal cancer; CCRT: Concurrent chemoradiotherapy; GTV: Gross tumor volume; 3DCRT: Three-dimensional conformal radiation therapy; IMRT: Intensity-modulated radiation therapy; OS: Overall survival; LRFFS: Locoregional failure-free survival; PFS: Progression-free survival; TNM: Tumor-node-metastasis

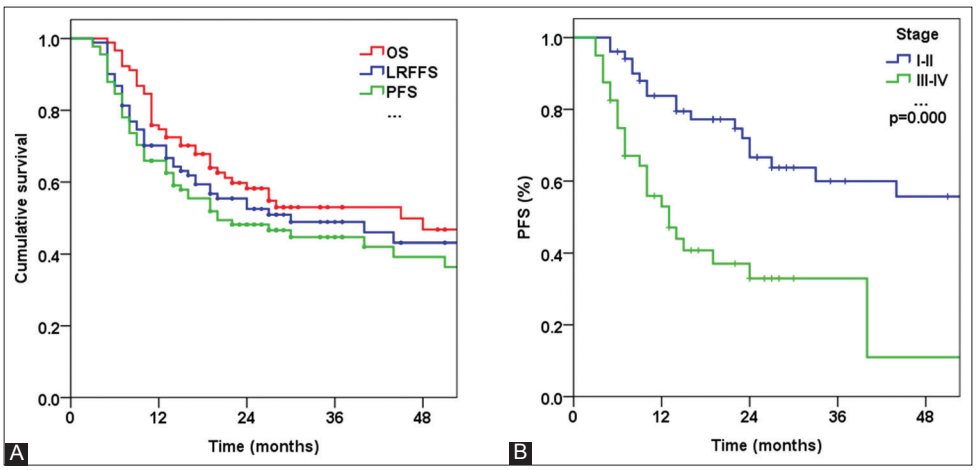

FIGURE 1. OS, LRFFS and PFS of 91 CEC patients (A). The two-year OS, LRFFS and PFS for all patients were 58.2%, 52.5% and 48.1%, respectively. Advanced clinical stage was a poor prognostic factor of PFS (B). CEC: Cervical esophageal cancer; OS: Overall survival; LRFFS: Locoregional failure-free survival; PFS: Progression-free survival.

TABLE 4. Outcomes of radiotherapy and surgery with larynx preservation in cervical esophageal cancer

Author (Reference)	Year	Number of patients	Regimen	Adjuvant protocol	Two-year survival	Three-year survival	Five-year survival
Radiotherapy							
Gkika et al. [5]	2014	55	CCRT	0%	35.0%	29.0%	25.0%
Cao et al. [33]	2015	64	IMRT	N/A	42.5%	N/A	N/A
Yamada et al [32]	2006	27	RT	40.7% (ST)	N/A	37.9%	37.9%
Burmeister et al. [36]	2000	34	CCRT	N/A	N/A	N/A	55.0%
Cao et al. [24]	2015	116	RT/CCRT	N/A	49.3%	N/A	N/A
Stuschke et al. [18]	1999	17	CCRT	35.3% (ST)	24.0%	N/A	N/A
Huang et al. [17]	2008	71	RT/CCRT	29.0% (ST)	35.0%	N/A	21.0%
Tong et al. [20]	2011	21	CCRT	23.8% (ST)	46.9%	N/A	20.0%
Suzuki et al. [19]	2014	20	NC+CCRT	25.0% (ST)	60.0%	N/A	30.0%
Surgery with larynx preservation							
Miyata et al. [6]	2013	58	Surgery±LP	N/A	N/A	49.6%	44.9%
Miyata et al. Subgroup [6]	2013	33	Surgery+LP	N/A	N/A	N/A	57.8%
Ott et al. [22]	2009	109	Surgery+LP	86.2% (NCR)	N/A	47.0%	47.0%
Kadota et al. [21]	2009	32	Surgery+LP	N/A	N/A	N/A	40.6%
Sun et al. [23]	2014	79	Surgery+LP	91.1% (ST)	N/A	66.4%	45.5%

NCR: Neoadjuvant chemoradiotherapy; NC: Neoadjuvant chemotherapy; AR: Adjuvant radiotherapy; ST: Salvage treatment; CCRT: Concurrent chemoradiotherapy; RT: Radiation therapy; IMRT: Intensity-modulated radiation therapy; LP: Larynx preservation; N/A: Not available.

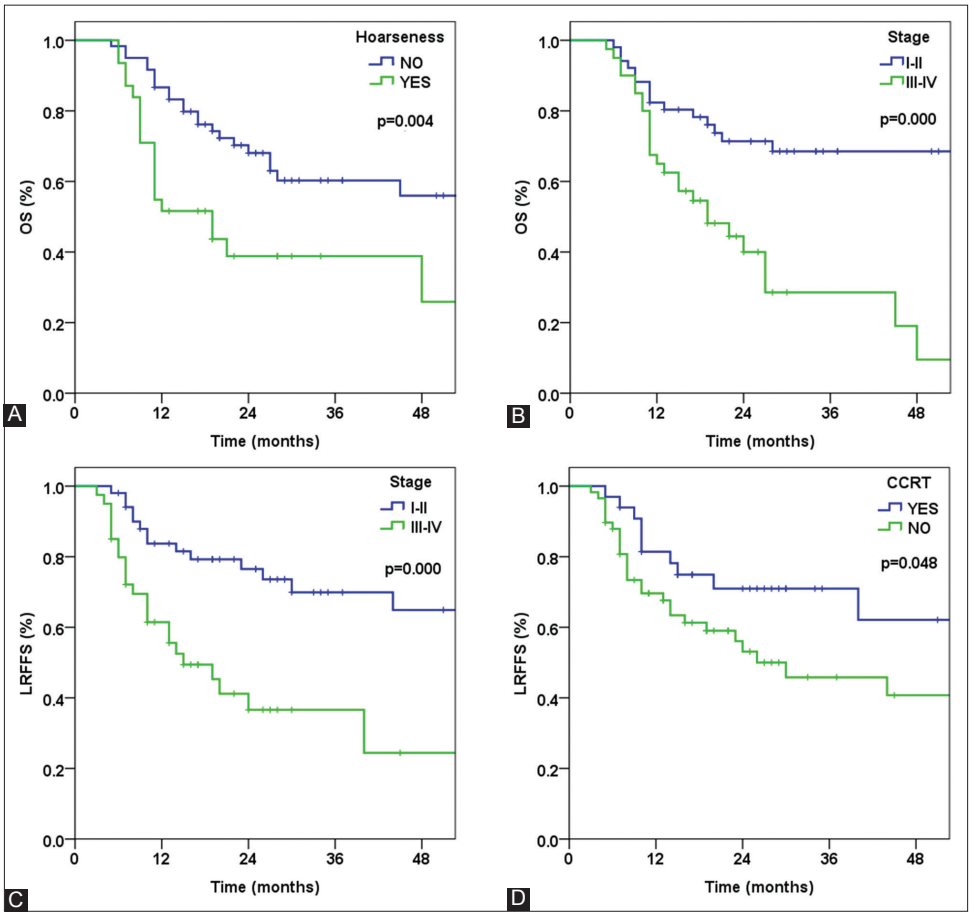

FIGURE 2. Hoarseness (A) and clinical stage (B) were independent prognostic factors of OS in CEC. Clinical stage (C) and CCRT (D) were independent prognostic factors of LRFFS. CEC: Cervical esophageal cancer; OS: Overall survival; LRFFS: Locoregional failure-free survival.

DISCUSSION

The management of CEC remains controversial. Prospective randomized data for CEC are lacking, due to its low incidence and a small number of clinical studies specifically investigating treatment outcomes and prognostic factors of survival in CEC patients. RT has become the primary treatment option for CEC, due to the fact that it allows preservation of the esophagus and adjacent organs. Nevertheless, studies investigating outcomes of CEC patients treated with

RT, CCRT, or surgery showed controversial results. For example, the two- and five-year survival rates of patients treated with CRT are 24% to 60% and 20% to 55%, respectively [5,17-20], while the five-year survival rates of CEC patients undergoing surgical resection with larynx preservation are higher, i.e. between 40.6% and 57.8% (Table 4) [6,21-23]. Moreover, 23.8% to 40.7% of CEC patients treated with CRT undergo salvage surgery [17-20]. On the other hand, other studies showed comparable disease control and survival between surgery with/without larynx preservation and RT with/without concurrent CT in CEC patients [7,20,24,25]. Chou et al. [7] retrospectively analyzed 15 patients who underwent radical resection (total laryngopharyngectomy with neck dissection, total esophagectomy, and reconstruction with stomach) and 14 patients who received CCRT. They showed no significant difference in the QOL and survival between the two treatment groups (mean survival time was 36.2 months for surgical resection vs. 34.4 months for CCRT [$p = 0.97$]) [7]. In a matched-case analysis of 58 patients with CEC, Cao et al. [24] did not show any significant differences in two-year survival rates between surgery group (in most cases pharyngolaryngoesophagectomy [PLE] was performed) and RT group (47.7% and 55.6%, respectively [$p = 0.71$]). Tong et al. [20] compared the outcomes of 107 CEC patients treated either with PLE (n = 62), upfront CCRT (n = 21), or palliative treatment (n = 24). The median survival duration was not statistically different between PLE and CCRT group in their study, i.e. 20 and 25 months respectively ($p = 0.39$) [20]. Liu et al. [25] performed a retrospective analysis of 57 patients with CEC who received PLE (n = 17) or definite CCRT (n = 40). The two groups were comparable for age, gender, American society of anesthesiologists (ASA) class and clinical stage. In a median follow-up of 14.4 months, the authors observed no significant difference in local recurrence rate (42.5% vs. 52.9%, $p = 0.469$), distant recurrence rate (32.5% vs. 29.4%, $p = 0.819$) and OS (17.1 vs. 14.4 months, $p = 0.943$) between CCRT and PLE groups. Among the above-described studies three performed PLE, thus increasing the possibility of a better therapeutic effect due to radical surgical approach. Furthermore, some studies reported that PLE is associated with high mortality rate and risk of complications in CEC patients [20,26-28]. Generally, a direct comparison between RT and surgery in CEC is difficult due to the retrospective design and inherent selection bias of these studies. In our study, the two-year OS, LRFFS and PFS of CEC patients treated with RT were 58.2%, 52.5% and 48.1%, respectively and only mild complications were recorded for these patients. Similar findings were reported by other studies [4,5]. Thus, CCRT appears to be optimal treatment strategy for CEC and should be considered individually.

Randomized studies on esophageal cancer [8] and squamous cell head and neck cancer [9,10] showed that CCRT results in organ preservation and improves patient OS compared with RT alone. A rationale for CCRT is that CT can sensitize tumors to RT by preferentially killing hypoxic cells, inhibiting tumor repopulation, inhibiting the sublethal radiation damage repair, and by improving blood supply and reoxygenation of organ [29]. However, in CEC, local and regional failure rates after CCRT remain high [1,29,30]. Studies with adequate follow-up reported a local relapse rate between 34% and 85% in CEC patients treated with CCRT [4,5,17,18,31,32] suggesting that a more aggressive local approach, such as the use of NAC or higher radiation doses, may be helpful. Our study showed that CCRT improved LRFFS in CEC patients. Several other studies on CEC patients reported a weak positive trend between OS or LRFFS and CCRT, although without significant difference compared to RT alone. Overall, CCRT may improve local tumor control in CEC patients [17,31,33]. In addition, Huang et al. [17] showed no significant difference in OS ($p = 0.94$) and LRFFS ($p = 0.19$) between patients treated with a lower dose, hypofractionated, 2D RT with 5-FU–based CT protocol and those treated with high-dose cisplatin-based, conventionally fractionated, conformal CCRT with prophylactic nodal RT.

Similar to previous studies [4,16,34], we showed that hoarseness was a significant prognostic factor for OS in CEC patients, i.e., it was associated with advanced clinical stage and disease progression. Hoarseness results from recurrent laryngeal nerve involvement due to direct tumor invasion or lymph node metastasis. Therefore, hoarseness can be considered as a late symptom of CEC and should be taken into account when planning the treatment.

Due to the low incidence of CEC, relatively short follow-up and patient heterogeneity, only a few studies have investigated the effect of advanced stage on survival in CEC. In the studies of Ludmir et al. [35] and Cao et al. [4] advanced stage had a significant impact on LRFFS and PFS in patients treated with definite RT or CCRT. In our study advanced clinical stage, together with hoarseness, was an adverse prognostic factor for OS, LRFFS and PFS. I.e., CEC patients with clinical stage I-II had a better OS (71.4% vs. 40.0%, $p = 0.000$), LRFFS (76.5% vs. 36.6%, $p = 0.000$) and PFS (72.0% vs. 32.9%, $p = 0.000$) compared to patients with stage III-IV. Moreover, CEC patients with advanced clinical stage with N1 and M1 (nonregional lymph node metastasis) tended to have a worse OS, LRFFS and PFS in our study.

The major limitations of our study are retrospective design, small number of included patients, selection bias, and heterogeneity among patients. Larger prospective randomized studies are necessary for better insight into the effect of CCRT on CEC.

CONCLUSION

In summary, 3DCRT and IMRT with concurrent CT is well-tolerated and may improve local tumor control in CEC

patients. Advanced clinical stage and hoarseness are adverse prognostic factors for OS, LRFFS, and PFS in CEC.

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DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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