Original Article

Long-term clinical outcomes and prognosis after definitive radiotherapy for patients with cervical esophageal squamous cell carcinoma: a single-institution retrospective study

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Background: Definitive radiotherapy has become a more common treatment for cervical esophageal squamous cell carcinoma (CESCC), but data about long-term clinical outcomes is still relatively sparse. The purpose of this study was to describe long-term clinical outcomes after definitive radiotherapy for CESCC, and identify the prognostic factors influencing these outcomes.

Methods: We retrospectively analyzed all patients who received definitive radiotherapy for CESCC at our institution between 2006 and 2014. The overall survival (OS) rate, locoregional failure-free survival (LRFFS) rate, and toxicities were retrospectively evaluated during long-term follow-up. Univariate and multivariate analyses were performed to identify prognostic factors.

Results: A total of 120 patients were included for analysis. The median prescribed radiation dose for the gross tumor and metastatic lymph nodes was 60 Gy. Elective nodal irradiation (ENI) was performed on 99 patients (83%); 90 patients (75%) received concurrent chemotherapy. The OS rates were 22.7% at 5 years and 14.9% at 8 years. The LRFFS rates at 3, 5, and 8 years were 27.5%, 21.7%, and 15.0%, respectively. The univariate analysis suggested that N classification and non-regional lymph node metastasis (M1Lym) status were independent risk factors for overall survival ($P<0.01$). A dose of more than 60 Gy didn't have a statistically significant influence in the multivariate analysis, although a total dose of more than 60 Gy was associated with improved survival in the univariate analysis. Concurrent chemotherapy was not associated with OS or LRFFS time in the univariate or multivariate analysis. A total of 74 patients (61.7%) experienced locoregional treatment failure. The most commonly documented acute toxicities were grade 1 and grade 2 toxicities in 61 patients (50.8%). There were 2 patients diagnosed with hypothyroidism as a late toxicity event.

Conclusions: Definitive radiotherapy is a reasonable curative treatment option with laryngopharyngeal preservation for CESCC patients. Radical treatments for lymph node metastases may improve the OS and LRFFS times. Monitoring for thyroid function may be warranted during long-term follow-up.

Keywords: Cervical esophageal squamous cell carcinoma (CESCC); definitive radiotherapy; hypothyroidism

Submitted Nov 21, 2023. Accepted for publication Dec 14, 2023. Published online Dec 22, 2023.
doi: 10.21037/jtd-23-1789
View this article at: https://dx.doi.org/10.21037/jtd-23-1789

Introduction

Cervical esophageal carcinoma, mainly cervical esophageal squamous cell carcinoma (CESCC), is a relatively uncommon malignant tumor representing 2.2–10.3% of all esophageal cancers (1-4). Owing to the abundant lymphatic drainage surrounding the cervical esophagus, and the unique anatomical position of the cervical esophagus between the lower border of the cricoid cartilage and the thoracic inlet, CESCC frequently exhibits extensive lymph node metastasis and invades adjacent structures, such as the hypopharynx rostrally and the thoracic esophagus caudally (5). Furthermore, CESCC is often locally advanced at diagnosis.

Radical surgery not only leads to recurrent nerve palsy and difficulty swallowing, which impair the patient's quality of life, but also is associated with early locoregional failure and poor prognosis (6-12).

In recent years, definitive radiotherapy has been reported to yield overall survival (OS) and local control rates comparable to those of surgery (13,14), and to contribute to organ preservation for patients with CESCC (15). The number of reports of definitive radiotherapy for CESCC is increasing year by year. However, previous reports on the value of radiotherapy for CESCC have included a small number of patients (6,13,15-25). In addition, few studies have had a long-term follow-up of more than 5 years (19-21,26). There are also discrepancies between the reports in terms of OS rates, locoregional recurrence, and major progression sites. The 5- and 10-year OS rates of patients undergoing definitive radiotherapy for CESCC have been (4) reported variously as 48.3% and 40.2% (26), 35.6% and 35.6% (21), and 25% and 10%, respectively (20). Locoregional and distant failure rates have been reported as 83% and 6% (26), 50% and 48% (19), 44% and 27% (20), and 10.8% and 5.9% (21), respectively. A report has concluded that different factors can influence survival prognosis, such as tumor stage, weight loss, hoarseness, delivered radiation dose, unresectable status, and non-regional lymph node metastasis (M1Lym) status (26). Due to the sparsity of studies, discrepant clinical results, and low incidence of cervical esophageal cancer, long-term follow-up studies are necessary to substantiate the value of radiation therapy for CESCC and to establish the prognostic factors for CESCC.

The purpose of this study was to present a comprehensive analysis of long-term clinical outcomes after definitive radiotherapy at a single institution and to explore the possible prognostic factors related to survival in patients with CESCC. This study will help to identify possible prognostic factors for CESCC related to long-term survival following definitive radiotherapy that may be useful for personalizing therapeutic approaches. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1789/rc).

Highlight box

Key findings

- This study was based on the rarity of cervical esophageal squamous cell carcinoma (CESCC) and to explore the considerable time span of the long-term follow-up with a large number of 120 patients which was not reported before.
- The purpose of this study was to present a comprehensive analysis of long-term clinical outcomes after definitive radiotherapy at a single institution and to show the possible prognostic factors related to survival in patients with CESCC.
- This study will help to identify possible prognostic factors for CESCC related to long-term survival following definitive radiotherapy that may be useful for personalizing therapeutic approaches in the real clinical practice.

What is known and what is new?

- The worse histological grade, more regional lymph node metastases and the "so-called" non-regional neck lymph node metastases are associated with the poor overall survival and locoregional failure-free survival (LRFFS) rate for CESCC.
- The local regional failure was the main pattern of failure for the CESCC.

What is the implication, and what should change now?

- The radical treatment for the lymph node metastases may improve the overall survival rate and LRFFS rate in the long-term follow-up.
- Definitive radiotherapy substantiated the cure treatment with laryngopharyngeal preservation for CESCC patients with a better life quality.
- More attention should be paid to the hypothyroidism after the radiation for CESCC in the long-term follow-up.

Methods

Inclusion criteria

This study was approved by the Ethics Committee of the Zhongshan Hospital, Fudan University (No. 2011-235) in September 2011. The study was performed in accordance with the Declaration of Helsinki (as revised in 2013), and written informed consent was provided by all participants and their family members. At the Department of Radiation Oncology, Zhongshan Hospital, Fudan University,

149 patients with cervical esophageal cancer underwent definitive radiotherapy between 2006 and 2014. Of these, 120 patients met the inclusion criteria and were included in this study.

The inclusion criteria were as follows: (I) a primary esophageal tumor was present in the cervical esophagus. The center of the primary tumor was located between the lower border of the cricoid cartilage [approximately 15 cm from the incisor teeth or based on computed tomography (CT) imaging] and the suprasternal notch (approximately 20 cm from the incisor teeth or based on CT imaging); (II) all biopsies of esophageal tumors were pathologically confirmed to be squamous cell carcinoma; (III) a dose of ≥50 Gy was prescribed for all gross tumors and metastatic lymph nodes with definitive intent; (IV) chemoradiation therapy was initiated between January 2006 and December 2014; (V) all treatments were approved, and informed consent was provided by all participants; (VI) all the follow-up visits were consecutive as of August 2018.

Materials and data collection

In this retrospective cohort study, medical information was extracted from medical records. The pretreatment workup included a complete medical history and physical examination, liver and renal function biochemistry, complete blood count, barium contrast study, endoscopic biopsy and pathological analysis, CT scans of the neck and thorax, positron emission tomography (PET) fusion with CT scans (available since September 2011, if necessary), details of radiotherapy and chemotherapy, and side effects.

The tumor location was categorized as follows: cervical esophagus alone, cervical esophagus with hypopharyngeal invasion, cervical esophagus with upper thoracic esophageal invasion, and cervical esophagus with invasion in both areas. The cervical periesophageal regional lymph nodes are the level VI and level VII lymph nodes, according to a head and neck map (27). M1Lym refers to supraclavicular lymph nodes (level IV lymph nodes) and/or cervical level III lymph nodes (26).

A multidisciplinary oncology team (surgeon, medical oncologists, and radiation oncologist) diagnosed the patients. Clinical staging was based on the tumor-node-metastasis (TNM) classification for esophageal cancer of the Union for International Cancer Control criteria (UICC; 7th edition, 2009) (28), after comprehensive assessment of the findings from the patient's physical and imaging examinations. Clinical T4 staging was mainly based on CT findings.

Radiotherapy planning and dose delivery

All radiotherapy plans were created with patients in a supine position. All patients were irradiated using conventional techniques by anteroposterior opposing fields or oblique fields (conventional radiation therapy, CRT), 3-dimensional conformal radiation therapy (3D-CRT), or intensity-modulated radiation therapy (IMRT) in a linear accelerator using 6–15-MV photon beams (3D-CRT and IMRT available from 2010).

The gross target volumes (GTV) were the primary tumor and metastatic lymph nodes. The clinical target volume of the primary tumor (CTVp) covered the primary tumor with an additional radial margin of at least 1 cm and longitudinal margins of at least 3 cm. Lymph node metastases were included in the radiation field. The clinical target volume of the metastatic lymph nodes (CTVlym) was created by adding a 0.5 cm margin. The GTV total dose was 50–70 Gy with a daily dose range of 2.0–2.3 Gy.

The cervical lymph node region field was included in the elective nodal irradiation (ENI), which involved level III, IV, and VI lymph nodes (29) and the paraesophageal and paratracheal lymph node regions of the upper mediastinum [level II was included if the hypopharynx was invaded (30)]; thus, all M1Lym were included in ENI and boost radiotherapy. The caudal extent of ENI was approximately 2 cm below the carina. For conventional irradiation therapy and 3D-CRT, the ENI dose was 40 Gy; for IMRT, the ENI dose was 40–50 Gy.

Chemotherapy

The chemotherapy regimen was based on platinum analogues (cisplatin or carboplatin). Before 2011, 5-fluorouracil and cisplatin were administered. Chemotherapy included intravenous 5-fluorouracil at a dose of 700 mg/m^{2}on days 1 to 4 and intravenous cisplatin at 70 mg/m^2 on day 1 and repeated every 4 weeks for 2 cycles at the beginning of radiation therapy; 2 additional cycles of chemotherapy with 5-fluorouracil (800 mg/m^2, days 1–5) and cisplatin (80 mg/m^2, day 1) were given at 4-week intervals 4 weeks after the completion of radiation therapy. After 2011, paclitaxel and cisplatin were administered. Paclitaxel (50mg/m^2) plus cisplatin (25mg/m^2) was administered weekly, starting concomitantly with radiotherapy and repeated every week for at most 6 cycles (the first course). After the completion of radiation therapy, 2 cycles of cisplatin (80 mg/m^2 on days 1 and 2) combined with paclitaxel (135 mg/m^2,

day 1) were administered to patients who were deemed able to receive chemotherapy drugs with a 3-week interval (the second course). During this period, the second course of chemotherapy was delayed until recovery if grade 3 toxicity developed. If adequate recovery was not achieved, the next course of chemotherapy was cancelled.

Adverse events and treatment monitoring

Pretreatment dysphagia was assessed with self-reports. Post-treatment dysphagia, radiation- or chemotherapy-induced toxicities, and late effects were assessed with the late effects in normal tissues (LENTs) analytic scales developed by the Radiation Therapy Oncology Group (RTOG) (31,32).

All patients were evaluated weekly during radiation. Ability to swallow, body weight, performance status, and related symptoms were evaluated daily. All patients were required to undergo follow-up after the completion of treatment: 1.5 months after the completion of treatment, every 3 months during the first 3 years, and every 6 months after 3 years. Each follow-up visit involved a complete examination including a hemogram and blood biochemical analysis, a barium contrast study, and CT scans of the neck and thorax.

The worst toxicity grade scored at any time was considered the final toxicity grade. Because radiation-related toxicities could present during treatment, the time to toxicity was calculated from the date of treatment initiation. Adverse events within 90 days after the initiation of chemoradiotherapy were considered acute toxicities. Side effects that occurred 3 months after the initiation of chemoradiotherapy were considered late toxicities.

Pattern of recurrence, locoregional failure-free survival (LRFFS), and OS

In our study, initial progression sites were categorized as locoregional areas, distant areas, or both. Locoregional failure was diagnosed if locoregional tumor persistence or recurrence of the primary tumor or neck lymph node metastases within the irradiated field was detected (19). Metachronous superficial esophageal tumors out of the radiation field (as secondary primary tumors) were not counted as locoregional progression events. LRFFS events were locoregional progression events and were censored on the date that locoregional control (LRC) was most recently verified. OS events included death from any cause and were censored at the final follow-up.

Statistical analysis

The baseline characteristics and disease factors were summarized with descriptive statistics in 120 patients. OS and LRC were calculated with the Kaplan-Meier method, and differences in LRC and OS among the categorical variables (e.g., age, M1Lym status, dysphagia grade, etc.) were assessed with the log-rank test. A Cox proportional hazard model was used for multivariate analysis (two-sided test with $P<0.05$ considered significant). The following parameters were included in the analysis: pretreatment factors including gender, pretreatment dysphagia, hoarseness, T-stage, N-stage, histological grade, and tumor invasion; and treatment factors including the chemotherapy protocol and dose of radiation. $P<0.05$ was considered statistically significant. All statistical analyses were performed in SPSS software (Version 22.0; IBM Corp., Armonk, NY, USA).

Results

Patient demographics and study population

We retrospectively identified 120 consecutive patients with squamous cell carcinoma who fulfilled the inclusion criteria. None of these patients had received antitumor treatment prior to radiation. The patients' ages ranged from 48 to 86 years with a median age of 62.5±8.38 years [median ± standard deviation (SD)]; 25.0% of patients (30/120) were aged ≥70 years. There were 81 male patients and 39 females, with a male to female ratio of 2.08:1. A total of 19 patients had stage T2 tumors (15.8%), 57 patients had stage T3 tumors (47.5%), and 44 patients had stage T4 tumors (36.7%). Lymph node metastases were detected in 96 patients (80.0%). At the time of diagnosis, 53 patients (44.2%) experienced grade 2 dysphagia, and 9.2% presented with grade 3 dysphagia. A total of 14 patients had paralysis of the recurrent laryngeal nerve before treatment. At the time of diagnosis, 47 patients had M1Lym, and 6 patients presented with a synchronous tumor (2 with laryngeal cancer, 1 with oropharyngeal cancer, 1 with thoracic esophageal cancer, and 2 with gastric cancer). The general characteristics of the enrolled patients are listed in *Table 1*.

Treatment outcomes

A total of 30 patients (age ≥70 years) did not receive chemotherapy, whereas 90 patients underwent concurrent chemotherapy. Chemotherapeutic regimens were based on platinum analogues (cisplatin or carboplatin) and

Table 1 Patient characteristics (n=120)

Parameters	No. of patients (%)
Age (years), median ± SD [range]	62.5±8.38 [48–86]
Gender	
Female	39 (32.5)
Male	81 (67.5)
Dysphagia grade*	
G0	14 (11.7)
G1	42 (35.0)
G2	53 (44.2)
G3	11 (9.2)
Hoarseness	
No	106 (88.3)
Yes	14 (11.7)
T classification	
T2	19 (15.8)
T3	57 (47.5)
T4	44 (36.7)
Histological grade	
1.00	76 (63.3)
2.00	24 (20.0)
3.00	20 (16.7)
N classification	
N0	24 (20.0)
N1	74 (61.7)
N2	22 (18.3)
M status (M1Lym)※	
No	73 (60.8)
Yes	47 (39.2)
Tumor extension	
CE	63 (52.5)
CE + HPI	12 (10.0)
CE + TEI	36 (30.0)
CE + HPI + TEI	9 (7.5)
Concurrent chemotherapy	
No	30 (25.0)
CDDP/CBP + 5-FU	37 (30.8)
CDDP/CBP + PTX	53 (44.2)
Type of radiation	
CRT	31 (25.8)
3D-CRT	24 (20.0)
IMRT	65 (54.2)
Total physical dose	
<60.0 Gy	26 (21.7)
≥60.0 Gy	94 (78.3)
Multiple primary carcinoma	
No	104 (86.7)
Synchronous	6 (5.0)
Metachronous	10 (8.3)

*, G0, none; G1, mild dysphagia but can eat a regular diet; G2, dysphagia requiring a predominantly puree, soft, or liquid diet; G3, dysphagia requiring intravenous hydration. ※, M status (M1Lym) indicates supraclavicular or cervical lymph nodal metastasis that was included in the irradiated field. SD, standard deviation; CE, cervical esophagus; HPI, hypopharyngeal invasion; TEI, thoracic esophageal invasion; CDDP, cisplatin; CBP, carboplatin; 5-FU, 5-fluorouracil; PTX, docetaxel; CRT, conventional radiation therapy; 3D-CRT, 3-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy.

5-fluorouracil or docetaxel. Of the 90 patients who received concurrent chemotherapy, 37 patients received cisplatin/carboplatin + 5-fluorouracil, but 12 patients did not complete the entire cycle; 53 patients received cisplatin/carboplatin + docetaxel, and 11 patients did not complete the entire cycle.

A total of 31 patients were irradiated via conventional techniques, with anteroposterior opposing fields or oblique fields at a daily dose of 2.0 Gy to the GTV. A further 24 patients received 3D-CRT at a daily dose of 1.8–2.0 Gy to the GTV. IMRT was received by 65 patients at a daily dose of 2.0–2.3 Gy to the GTV. The median radiation dose was 61.6 Gy (range, 50.0–70.0 Gy) for the primary tumor and metastatic lymph nodes. ENI was administered to 99 patients at a daily dose of 1.7–2.0 Gy to the CTV. The median total ENI dose was 41.25 Gy (range, 40.0–50.4 Gy).

Acute and late toxicities

The most commonly documented acute toxicities were grade 1 or grade 2 toxicities in 61 patients (50.8%)

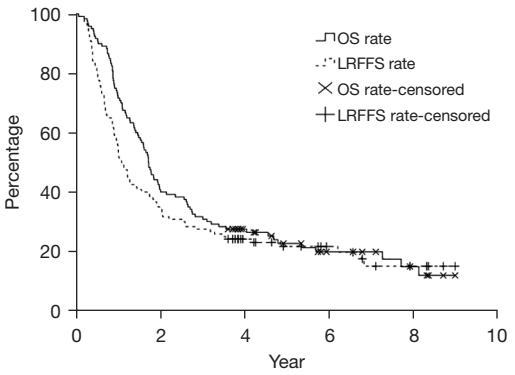

Figure 1 Kaplan-Meier curves for OS and LRFFS rates in the patients. LRFFS, locoregional failure-free survival; OS, overall survival.

including nausea, vomiting, mucositis, leukopenia, faint skin erythema or dry desquamation (ENI radiation field), and esophagitis, especially for those undergoing concurrent chemoradiation therapy. Grade 4 acute hematological (neutropenia) toxicities were experienced by 3 of the 90 patients undergoing concurrent chemoradiation therapy; none of the 30 patients who underwent only radiation therapy had grade 4 acute hematological toxicities. Grade 3 acute non-hematological toxicities (esophagitis and dysphagia) were observed in 4 patients. Grade 3 skin fibrosis, moist desquamation, and persistent pain were experienced by 1 patient, who required medication in the ENI radiation field without disease recession. No acute treatment-related deaths occurred.

Regarding late toxicities, all 24 patients who were still alive after more than 3 years had normal swallowing and no or mild (grade 1) esophageal symptoms. A total of 8 patients with grade 3 dysphagia underwent esophageal dilatation because of esophageal stricture or narrowing. Fistula occurred in 1 patient because of an anhydrous alcohol injection for progressive disease 2 years after treatment. Two patients developed symptomatic hypothyroidism 2 years after treatment, requiring lifelong thyroid hormone replacement.

Failure patterns

At the time of the last follow-up contact in August 2018, 96/120 patients had died. Among them, 3 patients died from accidental falls, 3 from pulmonary failure due to pneumonia, 2 from bone fractures, and 1 from kidney failure. A total of 74 patients (61.7%) experienced treatment failure that included only the tumor bed (38 involving the primary tumor and 23 involving the initial metastatic lymph nodes); 2 of these patients received a second course of radiation for the esophageal recurrence. Some 17 patients developed distant metastases: 7 patients had metastases in the lung (41.2%), 5 in other distant lymph nodes, 3 in bone, 1 in the liver, and 1 in the brain. Metachronous tumors were detected in 10 patients during follow-up 2 years after the completion of radiation therapy (3 patients with lung cancer, 2 with tongue cancer, 2 with gastric cancer, 2 with thoracic esophageal cancer, and 1 with rectal cancer).

OS, LRFFS and prognostic factors

At the time of the last follow-up in August 2018, 24 patients had survived. The OS rates at 1, 2, 3, 5, and 8 years were 72.5%, 40.8%, 31.7%, 22.7%, and 14.9%, respectively (*Figure 1*). The LRFFS rates at 1, 2, 3, 5, and 8 years were 55.8%, 35.0%, 27.5%, 21.7%, and 15.0%, respectively (*Figure 1*). Only 6 patients survived more than 8 years (5 were still alive in August 2018 and 1 was dead). The median OS and LRFFS times were 1.72 and 1.08 years, respectively. The long-term OS and LRFFS rates including the 3-, 5-, and 8-year survival rates are listed in *Table 2*, broken down according to the different prognostic factors.

The univariate analysis (*Table 2*) suggests that N classification and M1Lym status were significantly associated with OS and LRFFS. The 3- and 5-year OS and LRFFS rates of patients with M1Lym were significantly worse than those of patients without M1Lym (OS: 8.5% and 2.3% *vs.* 57.5% and 32.5%, P<0.001; LRFFS: 6.4% and 4.3% *vs.* 42.5% and 30.9%, P<0.001; *Table 2* and *Figure 2A,2B*). The 3-, 5-, and 8-year OS and LRFFS rates of patients without regional lymph node metastasis were better than those of patients with lymph node metastases (OS: P=0.021; LRFFS: P=0.032). The 3- and 5-year OS and LRFFS rates of patients who received doses of less than 60 Gy were significantly worse than those of patients who received doses of more than 60 Gy (OS: 26.9% and 19.2% *vs.* 34.0% and 28.1%, P=0.012; LRFFS: 17.6% and 10.4% *vs.* 29.8% and 19.8%, P=0.030). Hoarseness was associated with OS and LRFFS with a patient ratio of 7.571:1 (106:14).

The same clinical variables used in the univariate analysis were analyzed further in a multivariate analysis with backward logistic Cox regression selection. The associations between the variables and OS/LRFFS are detailed in *Table 3*. The multivariate analysis revealed that M1Lym status and

Table 2 Univariate analysis of prognostic factors influencing OS and LRFFS in patients with cervical esophageal cancer

Variables	OS (%)				LRFFS (%)			
	3-year	5-year	8-year	P value	3-year	5-year	8-year	P value
Age (years)				0.600				0.555
<70 (N=90)	29.8	18.2	9.1		23.4	19.1	11.5	
≥70 (N=30)	32.9	25.3	15.2		30.1	23.0	18.4	
Sex				0.735				0.750
Female	41.0	24.2	17.3		33.4	25.6	19.2	
Male	27.2	22.9	15.3		24.7	20.5	12.8	
Dysphagia grade				0.125				0.104
0–1	37.5	33.0	17.8		35.7	29.5	14.7	
2–3	26.6	20.3	14.1		26.6	17.2	15.0	
Hoarseness				0.010				0.017
No	35.8	29.9	13.5		31.1	24.5	17.0	
Yes	21.4	14.5	0.0		14.3	7.1	0.0	
T classification				0.391				0.636
T2	42.9	28.6	21.4		35.7	66.3	56.8	
T3	34.9	24.0	15.0		30.2	25.4	20.6	
T4	32.6	21.6	17.0		25.6	21.9	18.3	
Histological grade				0.095				0.091
1	32.3	23.6	20.7		30.7	23.7	15.8	
2	37.5	28.1	22.5		37.5	28.6	23.8	
3	23.8	9.5	0.0		14.3	4.8	0.0	
N classification				0.021				0.032
N0	83.3	64.5	36.8		70.8	52.3	43.6	
N1	24.3	18.9	8.3		24.3	16.2	10.8	
N2	27.3	13.6	4.5		18.2	4.5	0.0	
M status (M1Lym)				<0.001				<0.001
No	57.5	32.5	18.2		42.5	30.9	22.8	
Yes	8.5	2.3	0.0		6.4	4.3	0.0	
Tumor extension				0.055				0.063
No	50.8	44.4	27.6		46.6	37.6	19.8	
Yes	28.8	18.8	7.5		25.3	10.3	5.3	
Concurrent chemotherapy				0.839				0.828
No	30.0	22.5	11.3		30.0	25.0	12.5	
CDDP/CBP + 5-FU	35.1	24.3	11.6		29.7	21.6	18.9	
CDDP/CBP + PTX	28.3	20.4	15.3		24.5	20.8	16.2	

Table 2 (*continued*)

Table 2 (*continued*)

Variables	OS (%)				LRFFS (%)			
	3-year	5-year	8-year	P value	3-year	5-year	8-year	P value
Type of radiation				0.629				0.480
CRT	41.9	32.3	19.4		35.5	22.6	16.1	
3D-CRT	29.2	20.8	16.5		27.6	16.7	12.5	
IMRT	30.9	26.0	16.7		29.2	23.2	19.5	
Total physical dose				0.012				0.030
<60.0 Gy	26.9	19.2	15.4		17.6	10.4	0.0	
≥60.0 Gy	34.0	28.1	14.7		29.8	19.8	13.2	

OS, overall survival; LRFFS, locoregional failure-free survival; N, number of patients; M1Lym, non-regional lymph node metastasis; CDDP, cisplatin; CBP, carboplatin; 5-FU, 5-fluorouracil; PTX, docetaxel; CRT, conventional radiation therapy; 3D-CRT, 3-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy.

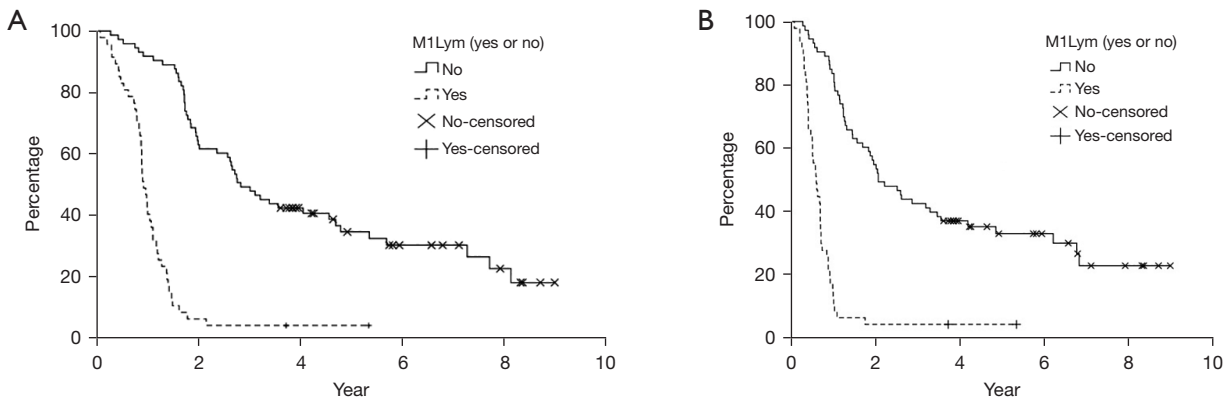

Figure 2 Kaplan-Meier curves for OS and LRFFS rates in patients with M status (M1Lym). (A) Kaplan-Meier curves for OS rates in patients with M status (M1Lym); (B) Kaplan-Meier curves for LRFFS rates in patients with M status (M1Lym). M1Lym, non-regional lymph node metastasis; OS, overall survival; LRFFS, locoregional failure-free survival.

N classification were significantly related to OS and LRFFS. The OS time continued to be worse for patients with M1Lym [hazard ratio (HR): 3.992; 95% confidence interval (CI): 2.317–6.879, P<0.001] and patients with regional lymph node metastases (HR: 3.527; 95% CI: 2.289–5.435; P<0.001) than for those without these features.

Although the univariate analysis found that patients who received a total dose of more than 60 Gy had better OS and LRFFS times than those who received smaller doses, there was no statistically significant influence of dose on OS or LRFFS time in the multivariate analysis (HR: 0.610, 95% CI: 0.368–1.012, P=0.056; HR: 0.784, 95% CI: 0.466–1.319, P=0.359). In addition, concurrent chemotherapy and type of radiation were not associated with OS or LRFFS time in either the univariate or the multivariate analysis.

Discussion

In this study, we analyzed a large number of patients with CESCC (n=120) who were treated with definitive radiotherapy and showed that the 2-year OS rate was 40.8%, similar to previously reported OS rates of 24.0–47.6% (15,33). In the long-term follow-up, the 5- and 8-year OS rates in our study were 22.7% and 14.9%, respectively, which are similar to the OS rates of 25% and 10% after definitive radiochemotherapy for locally advanced cervical esophageal cancers reported by Gkika *et al.* (20). However, our long-term 5- and 8-year OS rates were much lower

Table 3 Multivariate analysis of prognostic factors influencing OS and LRFFS in cervical esophageal cancer

Endpoint	HR (95% CI)	P value
OS		
Hoarseness (no/yes)	1.373 (0.786–2.398)	0.265
T classification (T2/T3/T4)	1.055 (0.728–1.529)	0.778
N classification (N0/N1/N2)	3.527 (2.289–5.435)	<0.001
M status (M1Lym) (no/yes)	3.992 (2.317–6.879)	<0.001
Histological grade (1/2/3)	1.284 (0.982–1.679)	0.068
Tumor extension (no/yes)	3.196 (1.897–5.386)	0.048
Total physical dose (<60.0/≥60.0 Gy)	0.610 (0.368–1.012)	0.056
LRFFS		
Hoarseness (no/yes)	1.056 (0.576–1.936)	0.859
T classification (T2/T3/T4)	1.429 (0.968–2.109)	0.072
N classification (N0/N1/N2)	3.269 (2.082–5.135)	<0.001
M status (M1Lym) (no/yes)	3.490 (2.034–5.988)	<0.001
Histological grade (1/2/3)	1.535 (1.159–2.034)	0.003
Tumor extension (no/yes)	3.982 (2.326–6.817)	0.057
Total physical dose (<60.0/≥60.0 Gy)	0.784 (0.466–1.319)	0.359

OS, overall survival; LRFFS, locoregional failure-free survival; HR, hazard ratio; CI, confidence interval; M1Lym, non-regional lymph node metastasis.

than the 48.3% and 40.2% reported by Sakanaka *et al.* (26). The resectable/unresectable status ratio for the patient cohort in Sakanaka *et al.*'s study was 10/20; thus, many patients in their study were in the early stages of disease and had a better prognosis (26). In contrast, in the present study, patients with primary tumor invasion into adjacent structures and M1Lym accounted for about 50% of the patient cohort; in these patients, the disease was at an advanced stage not suitable for surgery, which would explain the lower long-term OS rates observed.

Kang *et al.* (11) found that patients with cervical lymph node metastasis had a significantly lower OS rate than patients without cervical lymph node metastasis (22.7% *vs.* 58.2%) and a higher recurrence rate (45.9% *vs.* 16.3%). They concluded that cervical lymph node metastasis is a significant prognostic factor for CESCC patients and that patients with level IV lymph node metastasis exhibit the highest risk of metastasis (11). Sakanaka *et al.* (26) also reported that M1Lym was associated with poor OS and LRC rates (P<0.0001). The 5-year OS and LRC rates were 81.4% and 75.5%, respectively, for those with M0 stage disease versus 7.7% and 8.3% for those with M1Lym. In the present study, we showed that M1Lym status were significantly associated with OS and LRFFS in both the univariate and multivariate analyses (P<0.001) and that they are independent prognostic factors. Histological grade was also associated with LRFFS.

A recent study (34) reported that a large number of positive nodes and increasing N classification are associated with poor differentiation in esophageal cancers. The cervical esophagus has abundant lymphatic drainage and a unique anatomical position, which means that these tumors exhibit the highest risk of metastasis to the level IV neck lymph node area (M1Lym) (11). These findings are similar to our study results in that the worse the histological grade is, the higher the likelihood of developing regional lymph node metastases and non-regional neck lymph node metastases, which are associated with poor OS and LRFFS rates. Thus, control of cervical lymph node metastasis is a potential factor for OS and LRFFS in addition to control of the primary tumor.

In general, there is a positive dose–response relationship for definitive radiotherapy treatment: higher total doses produce better local control of tumors at all stages. However, this is not necessarily the case for CESCC when the dose is greater than 50.4 Gy. The RTOG 94-05 (35,36) revealed that a radiation dose higher than 64.8 Gy did not increase survival or LRC compared with a dose of 50.4 Gy. The results of the latest phase III multicenter, randomized, open-label clinical trial (37) showed that even a radiation dose of 40.0 Gy produced a 43.2% pathologic complete response rate. Cao *et al.* (15) observed no statistically significant difference in local failure-free survival (P=0.571) or regional failure-free survival (P=0.110) between patients who received doses of ≥66 and <66 Gy, although the 2-year OS rate was significantly better in CESCC patients receiving doses of ≥66 Gy (55.6% *vs.* 37.5%; P=0.018). Zhang *et al.* (16) observed no statistically significant difference in the 3-year OS, progression-free survival (PFS), or LRFFS between CESCC patients who received doses of ≥60 and <60 Gy (P=0.730, 0.964 and 0.631 for OS, PFS, and LRFFS, respectively). Herrmann *et al.* (38) also reported that there was no statistically significant difference in the 3-year OS, disease-free survival (DFS), or LRC between CESCC patients who received doses of ≥56 and <56 Gy (P=0.76, 0.78, and 0.88, respectively, for OS, DFS, and LRC). In our study, only 26 patients received a total dose of <60 Gy. This was either at the discretion of the

attending physician or because the patient refused further radiotherapy. Our univariate analysis showed a significant difference in the 5-year OS and LRFFS between those who received doses of ≥60 Gy and doses of <60 Gy (P=0.012 and 0.030, respectively, for OS and LRFFS). However, the results of the multivariate analysis showed no significant difference in OS and LRFFS with dose (P=0.056, HR: 0.610, 95% CI: 0.368–1.012; P=0.359, HR: 0.784, 95% CI: 0.466–1.319). More prospective trials are necessary to verify that escalating doses can improve OS or LRFFS for CESCC patients in the future.

Overall, we found long-term survival rates of 22.7% (5 years) and 14.9% (8 years), with good quality of life and swallowing function. Only 5 patients who were still alive at the last follow-up had survived without any disease progression. The long-term follow-up revealed that 2 patients had radiation-induced hypothyroidism after definitive radiotherapy. The thyroid gland was encompassed in the radiotherapy field (in the ENI radiation field in 99 patients). The incidence of radiation-induced hypothyroidism has been mentioned in several previous reports (15,25,26). Cao *et al.* (15) reported that 4 (2.5%) patients had hypothyroidism requiring lifelong thyroxine replacement. Yamada *et al.* (25) reported that 5 of 8 patients who survived more than 2 years had hypothyroidism. Sakanaka *et al.* (26) reported that the 5- and 10-year cumulative incidence rates of hypothyroidism were 31.6% (95% CI: 15.4–49.2%) and 62.5% (95% CI: 29.6–83.3%), respectively. Rønjom *et al.* (39) studied 203 patients with head and neck squamous cell carcinoma who received definitive radiotherapy at doses of 66–68 Gy and serial post-treatment thyrotropin assessments during follow-up. In a mixed model, the only independent risk factors for hypothyroidism were thyroid volume (cm^3) [odds ratio (OR) =0.75, 95% CI: 0.64–0.85, P<0.001] and mean thyroid dose (Gy) (OR =1.12, 95% CI: 1.07–1.20, P<0.001). From a mixed normal tissue complication probability model, the individual dose constraints for a 25% risk of hypothyroidism were 26, 38, 48, and 61 Gy for thyroid volumes of 10, 15, 20, and 25 cm^3, respectively. Rønjom *et al.* (39) further evaluated hypothyroidism after primary radiotherapy for head and neck squamous cell carcinoma with normal tissue complication probability modeling with latent time correction, and concluded that the thyroid dose constraints in treatment planning should be individualized based on thyroid volume. We strongly recommend that radiation oncologists be mindful of radiation-induced hypothyroidism as a late toxicity event and that routine thyroid function tests should be performed during long-term follow-up for patients with CESCC, especially for patients who survive more than 2 years after the completion of radiotherapy.

This study was retrospective because of the rarity of CESCC and the considerable time span of the long-term follow-up. There was significant heterogeneity in the study because of developments in TNM staging, radiotherapy techniques, concomitant chemotherapy regimens, and imaging over the time span of the study. Future prospective multicenter, randomized, open-label studies with larger populations and accurate standards are necessary to confirm our results for CESCC with long-term follow-up.

Conclusions

Definitive radiotherapy was associated with a favorable prognosis and laryngopharyngeal preservation in CESCC patients. M1Lym status and N classification were independent prognostic factors for OS and LRFFS. Radical treatments for lymph node metastases may improve the OS or LRFFS time. More attention should be paid to hypothyroidism after radiation for CESCC during long-term follow-up.

Acknowledgments

We thank the multidisciplinary team for esophageal cancer from the Department of Thoracic Surgery, the Department of Radiation Oncology, the Department of Medical Oncology, and the Department of Integrative Medicine at Zhongshan Hospital Fudan University for their cooperation and collaboration. We thank the follow-up team from the Radiation Oncology Department headed by Wenchao Zhu for the data collection and follow-up work at Zhongshan Hospital Fudan University.

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1789/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1789/dss

Peer Review File: Available at https://jtd.amegroups.com/

article/view/10.21037/jtd-23-1789/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1789/coif). J.Y.K. receives research support from Eli Lily, and serves on advisory board for AstraZeneca, outside the submitted work. The other 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. This study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (No. 2011-235). The study was performed in accordance with the Declaration of Helsinki (as revised in 2013), and written informed consent was provided by all participants and their family members.

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Cite this article as: Zhang S, Sun J, Pan X, Kim JY, Zhu W, Zhou Y. Long-term clinical outcomes and prognosis after definitive radiotherapy for patients with cervical esophageal squamous cell carcinoma: a single-institution retrospective study. J Thorac Dis 2023;15(12):6976-6987. doi: 10.21037/jtd-23-1789

