

Clinical Outcomes of Definitive Chemoradiotherapy for Cervical Esophageal Cancer

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Abstract. *Background/Aim:* To investigate the clinical outcomes of concurrent chemoradiotherapy (CCRT) in patients with cervical esophageal carcinoma and analyze the prognostic factors. *Patients and Methods:* Thirty-nine patients with cervical esophageal carcinoma were retrospectively identified among consecutive patients who received CCRT between November 2009 and September 2019 at our institution. The patients were treated by intensity-modulated radiation therapy (N=13) or three-dimensional conformal radiotherapy (N=26). *Results:* The median follow-up period was 35 months (range=2-158 months). There were 32 men and 7 women with a median age of 66 years (range=50-83 years). Clinical stages were I in 6 patients, II in 4, III in 19, and IV in 10. Hypopharyngeal invasion was noted in 8 patients. The initial treatment responses were evaluated 3-6 weeks after the final session of CCRT: a complete response (CR) in 24 patients, a partial response (PR) in 13, and stable disease (SD) in 2. Two- and 5-year overall survival (OS) rates were 73.8 and 59.4%,

respectively. Two- and 5-year progression-free survival (PFS) rates were 57.8 and 48.0%, respectively. A univariate analysis identified the initial treatment response (CR or non-CR) as a significant factor for OS ($p=0.0002$) and PFS ($p=0.0026$). The CR rate was 81.0% in patients with T1-3 and 33.3% in those with T4 ($p=0.0038$). *Conclusion:* Patients with cervical esophageal carcinoma in Nagasaki University Hospital in Japan achieved superior outcomes compared with previous studies. CR rate was higher in patients with T1-3 and correlated with better OS.

Esophageal carcinoma is the sixth leading cause of death from carcinoma worldwide (1). The esophagus is subdivided into three segments: cervical, thoracic, and abdominal. According to the UICC 8th TNM classification and staging system, cervical esophageal carcinoma is defined as that arising in the short part of the esophagus between the lower border of cricoid cartilage and the sternal notch. Cervical esophageal carcinoma only accounts for between 2-10% of esophageal carcinoma cases and the major histological type is squamous cell carcinoma (2). Surgical resection or concurrent definitive chemoradiotherapy (CCRT) are widely accepted as standard treatments for cervical esophageal cancer. However, surgical procedures for cervical esophageal cancer often require laryngopharyngectomy, which is usually associated with disruption of speech and usually compromises a patient's quality of life. Recently, the reports of definitive CCRT as a larynx preservation strategy for cervical esophageal cancer are increasing. Takebayashi *et al.* have suggested that definitive radiotherapy (RT) yields overall survival (OS) rates that are comparable with those after surgery (3). However, the number of previous reports of definitive CCRT for cervical esophageal cancer is still small. Furthermore, intensity-modulated radiation therapy (IMRT) has become widely used for cervical esophageal carcinoma,

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Key Words: Esophagus, esophageal neoplasms, chemoradiotherapy, radiotherapy, treatment outcome.

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Table I. Different chemotherapy regimens.

Chemotherapy regimen	N (%)
2 cycles of 5-Fluorouracil (700 mg/m ² /day on days 1-5) and Nedaplatin (130 mg/m ² /day on day 6)	17 (43.6)
2 cycles of Cisplatin (70 mg/m ² /day on day 1) and 5-Fluorouracil (700 mg/m ² /day on days 1-4)	15 (38.5)
2 cycles of Nedaplatin (100 mg/m ² /day on day 1) and 5-Fluorouracil (700 mg/m ² /day on days 1-4)	5 (12.8)
2 cycles of Docetaxel (60 mg/m ² /day on day 1)	1 (3)
Cisplatin (70 mg/m ² /day on day 1), 5-Fluorouracil (700 mg/m ² /day on days 1-4), Nedaplatin (100 mg/m ² /day on day 29), and 5-Fluorouracil (700 mg/m ² /day on days 29-32)	1 (3)

and can provide better dose coverage and conformity to the target volume than three-dimensional conformal radiotherapy (3DCRT), while minimizing excessive dose to normal organs, compared to 3DCRT. IMRT is recommended for cervical esophageal carcinoma because normal radiosensitive structures in the head and neck are close to the RT area. However, the superiority of IMRT over 3DCRT has not been clarified. Herein, we retrospectively investigated the clinical outcomes of CCRT in patients with cervical esophageal carcinoma in our institution, and analyze the prognostic factors, including RT technique.

Patients and Methods

Patients. Thirty-nine patients with cervical esophageal carcinoma were retrospectively identified among consecutive patients who received CCRT between November 2009 and September 2019 at Nagasaki University Hospital in Japan. All cases were confirmed histologically to be squamous cell carcinoma. Tumor staging was performed using the UICC 8th TNM classification and staging system. Patients with clinical stage IV based on supraclavicular lymph node metastases were analyzed because definitive RT was possible. The initial staging of patients was based on upper gastrointestinal endoscopy, computed tomography (CT), (18F) fluorodeoxyglucose positron emission tomography/CT (18F-FDG PET/CT), and barium contrast radiography. The Nagasaki University Hospital Review Board approved the present study (No. 22022130).

Treatment. RT. RT was delivered using 3DCRT (N=26) until October 2013, and subsequently IMRT (N=13) was adopted. RT was performed at a fractional dose of 1.8 or 2 Gy daily 5 times a week for all patients. The median dose was 63 Gy in 35 fractions (range=54-66 Gy in 30-35 fractions) using 3DCRT and 60 Gy in 30 fractions (range=60-66 Gy in 30-33 fractions) using IMRT. In patients treated with 3DCRT, elective nodal irradiation (ENI) was delivered to the lymph node areas from the upper cervical region to the subcarinal region at a dose of 39.6-41.4 Gy, whereas in patients treated with IMRT, ENI was delivered at a dose of 46 Gy.

Chemotherapy. All patients were treated with the following chemotherapy regimens. Twenty patients received 2 cycles of 5-

Table II. Patient and tumor characteristics.

	N (%)
Sex	
Male	32 (82.1)
Female	7 (17.9)
Median age (range)	66 (50-83)
WHO performance status	
0	4 (10.3)
1	31 (79.5)
2	4 (10.3)
T category	
T1	5 (12.8)
T2	3 (8)
T3	13 (33.3)
T4	18 (46.2)
N category	
N0	13 (33.3)
N1	20 (51.3)
N2	4 (10.3)
N3	2 (5)
M category	
M0	31 (79.5)
M1	8 (20.5)
Clinical stage	
I	6 (15.4)
II	4 (10.3)
III	19 (48.7)
IV	10 (25.6)
Hypopharyngeal invasion	
Yes	8 (20.5)
No	31 (79.5)
RT technique	
3DCRT	26 (66.7)
IMRT	13 (33.3)
Initial treatment response	
CR	24 (61.5)
PR	13 (33.3)
SD	2 (5)

WHO: World Health Organization; RT: radiotherapy; 3DCRT: three-dimensional conformal radiotherapy; IMRT: intensity modulated radiation therapy; CR: complete response; PR: partial response; SD: stable disease.

fluorouracil and nedaplatin at a 4- to 6-week interval. Seventeen patients received 2 cycles of 5-fluorouracil and cisplatin at a 4- to 6-week interval. One patient received 2 cycles of docetaxel at a 4-week interval. One patient received cisplatin on day 1, 5-fluorouracil on days 1-4, nedaplatin on day 29, and 5-fluorouracil on days 29-32. These chemotherapy regimens used are shown in detail in Table I. Following the completion of CCRT, 24 patients with adequate bone marrow function received adjuvant chemotherapy.

Follow-up. Initial treatment responses were assessed 3-6 weeks after the completion of CCRT. Radiation oncologists and gastroenterologists evaluated initial treatment responses using Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1. Patients were followed up every 3 months for at least 2 years, and then every 4-6 months thereafter. Endoscopy and/or CT was

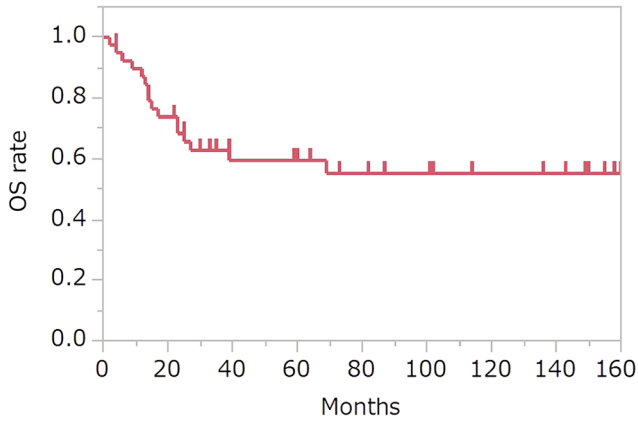


Figure 1. A Kaplan-Meier curve showing the overall survival (OS) of patients with cervical esophageal carcinoma.

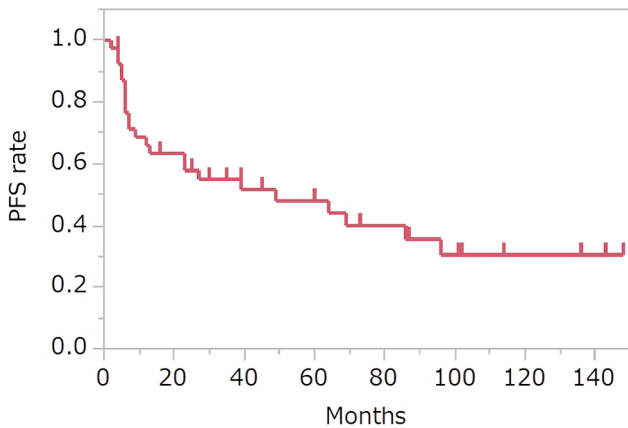


Figure 2. A Kaplan-Meier curve showing the progression-free survival (PFS) of patients with cervical esophageal carcinoma.

performed on each follow-up day. Endoscopy was performed to examine progression of the primary tumor. CT was used to assess progression of the regional lymph nodes and distant metastasis. 18F-FDG PET/CT were performed in patients with suspected recurrence. Acute and late toxicities were evaluated with The National Cancer Institute Common Toxicity Criteria ver. 5.0.

Statistical analysis. Initial treatment responses as well as OS and progression-free survival (PFS) were examined. OS was defined as the period from the first day of RT to the last day of follow-up or the date of death, and PFS as the time from RT to the last day of follow-up or the date of death or tumor progression. Survival rates were derived using the Kaplan-Meier method. Univariate analyses were performed using the Log-rank test to identify potential factors affecting OS and PFS after CCRT. The factors examined were sex (male or female), age (<66 or ≥66 years), the World Health Organization (WHO) performance status (0-1 or 2), T stage (T1-3 or T4), N category (N0 or N1-3), M stage (M0 or M1), clinical stage (I-III or IV), hypopharyngeal extension (Yes or No), total radiation

Table III. Univariate analysis of overall survival (OS).

	p-Value	
	OS	PFS
Sex	0.0792	0.1089
Male		
Female		
Age	0.4209	0.9100
<66		
≥66		
WHO performance status	0.9928	0.4074
0/1		
2		
T category	0.1861	0.4689
T1-3		
T4		
N category	0.5488	0.0540
N0		
N1-3		
M category	0.1620	0.6790
M0		
M1		
Clinical stage	0.5184	0.6424
I-III		
IV		
Hypopharyngeal invasion	0.3213	0.0809
Yes		
No		
Total radiation dose (Gy)	0.4320	0.6441
<63		
≥63		
External beam radiotherapy techniques	0.7549	0.4336
3DCRT		
IMRT		
Adjuvant chemotherapy	0.1428	0.4142
Yes		
No		
Initial treatment response	0.0002	0.0026
CR		
Non-CR		

PFS: Progression-free survival; WHO: World Health Organization; 3DCRT: three-dimensional conformal radiotherapy; IMRT: intensity modulated radiation therapy; CR: complete response.

dose (<63 or ≥63 Gy), RT technique (3DCRT or IMRT), adjuvant chemotherapy (Yes or No), and initial treatment responses (complete response (CR) or non-CR). *p*-Values <0.05 indicated a significant difference. Categorical variables were described as absolute values and percentages. Fisher’s exact test was used to compare initial treatment responses between T1-3 and T4. All statistical analyses were performed using JMP (SAS Institute, Cary, NC, USA).

Results

Treatment outcomes. Patient characteristics are summarized in Table II. The median follow-up period was 35 months (range=2-158 months). All patients completed RT with a

Table IV. Summary of recent studies on concurrent chemoradiotherapy (CCRT) for patients with cervical esophageal carcinoma.

First author (reference)	Year	N	Dose (Gy)	CCRT (%)	2y-OS (%)	5y-OS (%)
McDowell (4)	2017	37	70	100	53.0	NA
Kumabe (5)	2017	37	60-70	100	NA	35.6
Sakanaka (6)	2018	30	60-61.5	86.7	NA	48.8
Dai (7)	2019	106	50-70	65.1	46.2	28.3
Zhang (8)	2022	156	44-72	87.8	55.1	33.3
Present study		39	54-66	100	73.8	59.4

2y-OS: 2-Year overall survival; 5y-OS: 5-year overall survival; NA: not available.

median duration of 52 days (range=41-86 days). Two- and 5-year OS rates were 73.8 and 59.4%, respectively (Figure 1), while 2- and 5-year PFS rates were 57.8 and 48.0%, respectively (Figure 2). The potential of various factors to predict OS and PFS were examined, and the results obtained are shown in Table III. The univariate analysis identified the initial treatment response (CR or non-CR) as a significant factor for OS ($p=0.0002$) and PFS ($p=0.0026$). Five-year OS rates were 78.3 and 28.9% for CR and non-CR, respectively and five-year PFS rates were 66.2 and 0% for CR and non-CR, respectively. The CR rate was 81.0% (17/21) in patients with T1-3 and 33.3% (6/18) in those with T4; the difference was statistically significant ($p=0.0038$).

Failure patterns and second-line treatments. Recurrence was detected in 22 patients in the follow-up period. The median recurrence time was 8 months (range=2-96 months). Initial failure patterns were as follows: 13 patients with local recurrence only, 1 with local recurrence and regional lymph node metastases, 1 with local recurrence and distant metastases, 3 with regional lymph node metastases only, and 4 with distant metastases. Failure patterns were classified as locoregional recurrence or distant metastasis. Locoregional recurrence was defined as local recurrence and/or regional lymph node metastases, whereas distant metastasis was defined as progression outside of the prophylactic area. Two out of the 17 patients with locoregional recurrence underwent salvage surgery, and one patient was cured and is currently alive for more than 6 years. The other patient developed distant metastases after salvage surgery and was treated with chemotherapy followed by immune checkpoint inhibitors (ICIs). Endoscopic submucosal dissection (ESD) was also performed for 3 patients and photodynamic therapy (PDT) for 2, and all were cured and remain alive with preservation of the larynx. Furthermore, 4 patients were treated with chemotherapy, while the remaining 3 did not receive any additional anticancer treatment.

Acute and late toxicities. Two and nine patients developed acute hematological toxicity grade 3 and 4 events

(neutropenia), respectively. An acute non-hematological toxicity grade 3 event caused by RT (esophagitis, anorexia, and dysphagia) was detected in 6 patients. None of the patients exhibited symptomatic radiation pneumonitis or pericarditis/pericardial effusion. Furthermore, neither \geq grade 3 esophageal stricture nor \geq grade 1 fistula formation was observed as a late toxicity in patients without disease progression. These patients did not require permanent gastrostomy feeding tubes or temporary tracheostomy tubes because of radiation-related late toxicity. Nine patients underwent venous blood sampling after RT to assess thyroid functions, and 7 had developed grade 2 hypothyroidism during the follow-up period.

Discussion

Recently, the reports of definitive CCRT as a larynx preservation strategy for cervical esophageal cancer are increasing. However, its clinical efficacy has not yet been examined in detail (4-8). Mature follow-up data on CCRT for cervical esophageal carcinoma are summarized in Table IV. In these studies, 2- and 5-year OS rates were 46.2-55.1% and 28.3-48.8%, respectively. In the present study, 2- and 5-year OS rates were 73.8 and 59.4%, which were better than those previously reported. We suggested one major reason for this better survival rate. There was a difference in the rate of successful salvage treatment. Sakanaka *et al.* (6) reported that only 4 of 17 (23.5%) patients with locoregional recurrence could receive surgery as salvage treatment. In our study, 7 of 17 (41.1%) patients with locoregional recurrence could receive salvage treatment; surgery in 2 patients, ESD in 3 patients, and PDT in 2 patients. In our institution, we performed the follow-up endoscopy with short interval after CCRT to detect local recurrence in the early stages. The patients with early-stage recurrence received salvage ESD or PDT, which may have contributed to the favorable prognosis.

We examined prognostic factors of CCRT for cervical esophageal carcinoma at our institution. CR was more frequent in patients with T1-3 and survival correlated with CR. Similar findings were reported by Aoyama *et al.* (9),

who identified CR as the most important prognostic factor following definitive CCRT. If salvage surgery represents an option for non-CR, further improvements in treatment efficacy may be expected. Ogino *et al.* (10) found abdominal lymph node metastasis diagnosed by 18F-FDG PET/CT was a worse prognostic factor for esophageal carcinoma patients treated with CCRT. For cervical esophageal carcinoma, abdominal lymph node metastasis is quite rare (11). Therefore, CCRT for cervical esophageal carcinoma might be more effective treatment. In our study, there is no patients with locally advanced esophageal carcinoma with esophageal perforation. These patients need immediate treatment, such as esophagectomy or stent therapy, and it is difficult to perform CCRT. Ohsawa *et al.* (12) suggested CCRT after esophageal bypass surgery in a patient with locally advanced esophageal carcinoma with esophageal perforation. This is a potential treatment option to improve treatment outcomes and quality of life. No significant difference was observed between the 3DCRT and IMRT groups. Yang *et al.* (13) found no significant differences in OS or failure-free survival (FFS) between patients treated with IMRT and those treated with 3DCRT. In contrast, Ito *et al.* (14) showed significantly longer OS with IMRT than with 3DCRT. The sufficient salvage rate was also higher with IMRT than with 3DCRT when locoregional recurrence was presented, which contributed to the difference in OS. Furthermore, neither locoregional control nor PFS significantly differed between IMRT and 3DCRT. Consistent with previous findings, the present results do not support the survival advantage of IMRT over 3DCRT.

In our study, one patient received ICIs as a treatment for distant metastases. Recent studies reported the potential of ICIs to improve survival outcomes in patients with esophageal cancer (15-17). The synergistic effects of ICIs combined with radiation have been attracting increasing attention. Preclinical studies revealed the up-regulated expression of PD-L1 in irradiated tumors. Based on these findings, combination therapy with anti-PD-1 antibodies and radiation, which exerts enhanced antitumor effects, needs to be applied to locally advanced esophageal carcinoma (18). Radiation has been suggested to promote the presentation of antigens on tumor cells, and this is one of the rationales supporting the validity of its combination with ICIs (19). Phase 3 trials are now underway to examine the efficacy of various combinations of ICIs with cytotoxic agents and radiation for the treatment of esophageal cancer [NCT03430843, NCT03143153 (CheckMate 648), NCT03829969 (JUPITER 06)]. The findings obtained may result in a paradigm shift in practical strategies for the treatment of esophageal carcinoma.

Limitations. This was a single institutional retrospective study with a small number of patients treated with various chemotherapy regimens and RT doses and fields.

Conclusion

Patients with cervical esophageal cancer treated by CCRT at our institution achieved superior outcomes compared with previous studies. CR rate was higher in patients with T1-3 and correlated with better OS.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

Yutaro Tasaki: Conceptualization, formal analysis, writing. Takuya Yamazaki: Validation, writing. Shuhei Miyazaki: Software. Tatsuya Takeda: Methodology, investigation. Mika Nakatake: Formal analysis. Asuka Takahira: Validation. Koichi Honda: Validation. Daisuke Nakamura: Visualization, resources. Akiko Egawa: Investigation. Kazuto Ashizawa: Formal analysis, resources, supervision, validation, investigation. All Authors have read and agreed to the published version of the manuscript.

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Received September 27, 2022

Revised October 13, 2022

Accepted October 14, 2022