Multimodal Approach for Cervical Esophageal Carcinoma: Role of Neoadjuvant Chemotherapy

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Abstract. *Aim: To examine the outcome of patients with cervical esophageal cancer treated by a multimodal protocol. Patients and Methods: We retrospectively analyzed the outcome and prognostic factors for 20 patients with cervical esophageal cancer who received multimodal treatment at the Kurume University Hospital between 2003 and 2009. One case of stage I, seven of stage II and 12 of stage III disease (2 T1, 3 T2, 4 T3, 11 T4 and 14 N1) were included. Radiotherapy was administered at a median dose of 60 Gy (range=30-70 Gy). The median follow-up time was 32 months for surviving patients (14-94 months). Platinum-based neoadjuvant chemotherapy (NAC) was performed in 14 cases and all received chemoradiotherapy. Results: median survival was 20 months and overall survival rates at 1, 2, and 5-years were 70%, 60% and 30%, respectively. T-Category, length of the primary lesion, N-category, stage, hemoglobin levels and response to induction chemotherapy were statistically significant predisposing factors for overall survival rate. According to NAC response, 10 good responders (complete response or partial response) showed 2-year survival rates of 80% (5 survivors), whereas that for poor responder (stable disease and progressive disease) was 0% (p=0.006), respectively. Response to NAC was the only statistically significant predisposing factor for increased progression-free survival (p=0.03). Severe acute toxicities of grade 3 or more appeared in 5 patients; two grade 5 (esophageal perforations and lung fistula), one grade 4 (bilateral recurrent nerve palsy), and two grade three (pneumonitis and mucositis). Conclusion: Although severe prognosis was identified for cervical esophageal cancer, good response to NAC indicates a good prognosis with organ preservation even for those with T4 tumor.*

Cervical esophageal cancer is relatively uncommon, representing less than 5% of all esophageal cancers (1). The management of cervical esophageal cancer is controversial. Although surgical resection with or without postoperative radiotherapy (CRT) has been the mainstay of treatment since the early 20th century, surgery requiring laryngopharyngo-esophagectomy is usually associated with disruption of speech and swallowing, and compromises a patient's quality of life. Advances in non-surgical therapies have arisen out of a need to treat the majority of patients with esophageal cancer with the intention of organ preservation, or those who do not have a surgical option because of cancer stage or comorbidity (2-9). Neoadjuvant chemotherapy (NAC) and concurrent chemoradiotherapy (CCRT) has been used for organ preservation for locally advanced head and neck squamous cell carcinoma, and also for cervical esophageal cancer (3, 8, 10-13). We, therefore, present our preliminary outcomes for organ-preserving strategies including NAC for cervical esophageal cancer.

Patients and Methods

Twenty-four patients with cervical esophageal cancer were treated with multimodal treatment at Kurume University Hospital between 2003 and 2009. Four cases were excluded from analysis because of palliative intention due to distant metastasis, older age, or poor general condition. The patients' characteristics are summarized in Table I. A total of 13 males and 7 females with age ranging from

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Table I. *Patients' characteristics.*

Variable		Value
Gender, n	Male	13
	Female	7
Age, years	Median (range)	64 (44-74)
Site, n	Ce	12
	Ce+MT	3
	Ce+UT	4
	CE+Ph	1
T-Category, n	1	2
	2	3
	3	4
	4	11
N-Category, n	0	6
	1	14
Stage, n	I	1
	II	7
	III	12
Tumor length	Median (range)	4 cm (2-12.5 cm)
Hemoglobin level	Median (range)	12.4 g/dl (9.1-14.1 g/dl)
Neoadjuvant chemotherapy, n	Yes	14
	No	6

Ce: Cervical esophagus; MT: middle thoracic esophagus; UT: upper thoracic esophagus; Ph: hypopharynx.

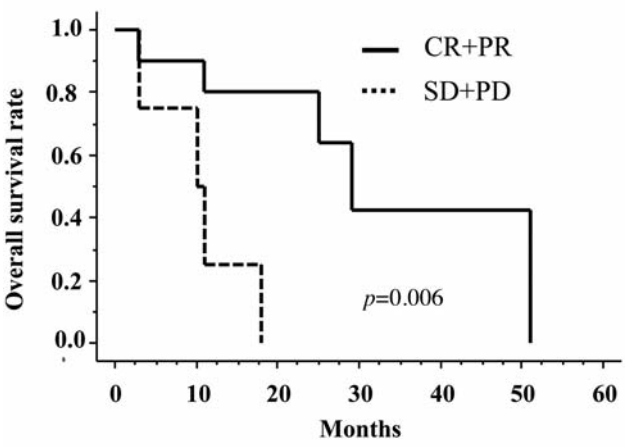

Figure 1. *Influence of response to neoadjuvant chemotherapy (NAC) on survival. According to NAC response, ten good responder (complete response CR or partial response PR; solid line) showed 2-year survival rates of 80% (five survivors), whereas four poor responders (stable disease SD + progressive disease PD; dotted line) showed 0% (p=0.006), respectively.*

44 to 74 years (median=64) years were included. Tumors were staged according to the sixth version of Union for International Cancer Control (UICC2002) (14). One stage I, 7 stage II and 12 stage III diseases (2 T1, 3 T2, 4 T3, 11T4 and 14 N1) were included. External-beam RT (1.8-2.0 Gy/day) was administered 5-10 times a week in once-daily (1.8-2.0 Gy/day) or twice-daily fractions (1.2 Gy twice) using a 4-10 MV photon beam produced by a Linac MHCL 15DP (Mitsubishi Co., Tokyo, Japan). Median irradiated dose was 60 Gy (30-70 Gy). A radiation planning system for 3-D conformal RT was used to schedule treatments. RT (up to 40-46 Gy) was initially administered with anterior-posterior T-shaped parallel opposed field to the primary, and supraclavicular regions. The primary lesion and involved neck nodes were further boosted to 60-70 Gy with oblique parallel opposed fields to spare the spinal cord. The gross tumor volume (GTV) was defined as the total volume of the primary lesion and the involved lymph nodes and was determined using laryngoscopy, computed tomography (CT), magnetic resonance imaging (MRI), and 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG) positron-emission tomographic (PET) scans. A positive lymph node was defined as >10 mm in the short axis on CT/MRI or positive by ^{18}F-FDG PET findings. Out of the 20 patients, 14 patients underwent multi-agent NAC consisting of 13 treated with cisplatin and 5-fluorouracil (5-FU) (FP) and one with FP followed by cisplatin, 5-FU and docetaxel (TPF). All patients received concurrent FP, and one with intra-arterial infusion chemotherapy. All patients were enrolled in this study after obtaining written informed consent prior to treatment in accordance with the guidelines of the Institutional Review Board. Patients were followed-up every month during the first six months and every 3-6 months thereafter. The median follow-up time was 25 (range=3-94) months for all patients, or 32 months for surviving patients (14-94 months). Acute and late toxicities were scored according to the Common Terminology Criteria of Adverse Events, version 3.0 (15). Local control (LC), progression-free survival (PFS), laryngeal preservation (LP) and overall survival (OS) rates were examined.

Statistical analysis. All statistical analyses were performed using the Stat-view 5.0 statistical software (SAS Institute, Inc., Cary, NC, USA). Frequencies were analyzed using the χ^2 test. Means were compared using the Student's t-test for normally distributed data and Mann–Whitney *U*-test for skewed data. Survival data and cumulative incidences were estimated by the Kaplan–Meier method and examined for significance using the log-rank test. Cox's proportional hazard model was used for the multivariate analysis. Cutoff values were set as the average or median value of each variable unless otherwise stated. We set a cut-off value of hemoglobin at 11.5 g/dl based on our previous study of hypopharyngeal cancer (16). All analyses used the conventional $p<0.05$ level of significance.

Results

Twenty patients were treated with chemoradiation therapy. Two cases stopped chemoradiotherapy at 30 Gy due to progressive disease or grade 4 bilateral recurrent nerve palsy after intra-arterial infusion chemotherapy. One more case discontinued radiotherapy at 46 Gy due to esophageal fistula. OS (and LP) at one, two, and five years were 70%: 14 survivors, (65%: 11 censors), 60%: 9 survivors (65%: 9 censors) and 30%: 2 survivors (41%: 2 censors). According to T classifications, LC (and PFS, LP, OS) at two years were 100%: 2 censors (100%: 1 censor, 100%: 1 censor, 100%: one survivor), 67%: 2 censors (33%, 100%: 2 censors, 67%:

Table II. *Analysis of prognostic factors in therapy of cervical esophageal cancer.*

Variable		n	At 2 years			Univariate (*p*-value)		
			LRC	PFS	OS	LRC	PFS	OS
Age	≥68 years	10	40%	40%	60%	0.92	0.32	0.53
	<68 years	10	30%	20%	60%			
Gender	Male	15	33%	33%	47%	0.81	0.77	0.16
	Female	5	40%	20%	100%			
T-Category	1-3	9	56%	44%	76%	0.09	0.22	0.02
	4	11	18%	18%	44%			
N-Category	0	6	50%	33%	100%	0.33	0.66	0.04
	1	14	29%	29%	43%			
Stage	I-II	8	63%	50%	86%	0.02	0.084	0.0063
	III	12	17%	17%	40%			
Length of lesion	<3 cm	6	50%	44%	80%	0.15	0.22	0.03
	>3 cm	14	29%	18%	49%			
Site	Ce only	12	33%	33%	64%	0.93	0.64	0.4
	Ce and other subsite	8	38%	37%	50%			
Hemoglobin level	≥11.5 g/dl	15	47%	40%	65%	0.05	0.06	0.04
	<11.5 g/dl	5	20%	0%	40%			
Irradiated dose	≥60 Gy	6	36%	29%	49%	0.71	0.49	0.27
	<60 Gy	14	33%	33%	53%			
NAC	Positive	14	21%	14%	55%	0.05	0.09	0.12
	Negative	6	67%	67%	67%			
Response to induction chemotherapy	CR + PR	10	30%	20%	80%	0.01	0.03	0.006
	SD + PD	4	0%	0%	0%			

NAC: Neoadjuvant chemotherapy; PFS: progression-free survival; OS: overall survival; LRC: locoregional control rate; LPR: laryngeal preservation rate; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

two survivors), 25%: one censor (25%: 1 censor, 25%: 1 censor, 75%: one survivor), and 18%: 2 censors (18%: 2 censors, 63%: 4 censor, 44%; three survivors) for T1, T2, T3, T4 diseases. Outcome of analysis on predisposing factors are shown in Table II. Low T-category, short length of primary lesion, low N-category, low stage, hemoglobin level ≥11.5 g/dl and response to induction chemotherapy (Table II), were statistically significant factors for OS. Response to NAC was the only statistically significant factor predicting better PFS. Lower stage and response to NAC were statistically significant factors predictive of better LC. According to NAC response, ten good responders (complete response or partial response) showed 2-year survival rate of 80% (five survivors), whereas that for poor responders (stable disease and progressive disease) was 0% (p=0.006), respectively (Figure 1). In multivariate analysis, we did not find any statistically significant factors predictive of OS, LC and PFS. There was borderline statistically significant difference in the LC between the NAC group and group without NAC. This is to be expected because we used NAC for advanced disease (NAC-positive=3 stage II and 11 stage III vs. NAC-negative=1 stage I, 4 stage II and 1 stage III, p=0.02). Initial recurrences were 14 local recurrences with seven simultaneous lymph node recurrences. Lymph node-only recurrence was found in two cases. Salvage surgery was performed for five cases with three successful outcomes. Severe acute toxicities appeared in 5 cases; one grade 5 esophageal perforation, one grade 5 lung fistula, one grade 4 bilateral recurrent nerve palsy, two grade three toxicities (pneumonitis and mucositis).

Discussion

Cervical esophageal cancer has poor prognosis even after curative resection. Reported actuarial OS rates of cervical esophageal cancer treated by surgery/chemotherapy and/or radiotherapy at 2 years was 24-47.6% (2, 5-9, 17, 18), which our data concord with. After induction chemotherapy (NAC) by Vermorken *et al*. in squamous cell carcinoma of the head-neck area (12, 13), similar tactics were explored in cervical esophageal carcinoma. Our data confirm that this strategy could be applied to cervical esophageal cancer. We here show that the response to NAC is a useful indicator for better survival with organ preservation even for T4 cases.

On the contrary, there are several problems left in our study. Firstly, the new data raise the question as to which combination induction chemotherapy should be recommended (actually, a combination of docetaxel, cisplatin and 5-

fluorouracil; TPF). As we used FP in almost all cases, there should be a need to examine more modern chemotherapy combinations with and without concurrent radiation in trials. Secondly, there is a room for improve outcome especially for poor responders because nearly all poor responders within a few years, with considered toxicities. To improve quality of life and outcome of those patients, there is a need for new strategies. Firstly is that for a reduction of toxicity, *e.g.* bioradiotherapy using a less toxic protocol (*e.g.* cetuximab). Next is to enhance treatment intensity through new drug exploration or radiation dose escalation with modern techniques such as intensity-modulated radiation therapy (2) and early surgical intervention if possible.

In conclusion, although severe prognosis was identified for cervical esophageal cancer, response to NAC is a good surrogate of survival with organ preservation even for cases with T4 tumors.

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