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ORIGINAL ARTICLE

Treatment results of radiotherapy for carcinoma of the cervical esophagus

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Abstract

The methods and results of treatment for cancer of the cervical esophagus differ from those for cancer of the thoracic esophagus. Our objective was to retrospectively review the outcome for cervical esophageal cancer patients treated with radiotherapy. Twenty-seven patients with carcinoma of the cervical esophagus treated with definitive radiotherapy from 1988 to 2002 were enrolled in the study. Clinical stage (UICC 1997) was stage I in five, II in six, III in 12 and IV in four. Concurrent head and neck malignancy was found in six patients (22%). The mean radiation dose was 66 Gy. Concurrent chemotherapy (cisplatin and 5-fluorouracil) was performed in 23 patients. The actuarial overall survival rates at 1, 3 and 5 years were 55.6%, 37.9% and 37.9%, respectively, with a median survival of 13.9 months. In the patients with stage I, the 3-year and 5-year survival rates were 75% and 75%, respectively. With univariate analysis, only two of the possible prognostic factors were found to actually influence survival: performance status ($p < 0.01$) and tumor length ($p < 0.01$). The survival of patients with cervical esophageal cancer remains poor. It is thought that organ preservation is possible by definitive chemoradiation for early cancer.

Carcinoma of the cervical esophagus is relatively uncommon, representing less than 5% of all esophagus cancer [1]. Limited information is available on the results of treatment of cervical esophageal cancers, because they have often been included with carcinomas of the hypopharynx, especially when it comes to reports on surgical management. The methods and results of treatment for cancer of the cervical esophagus differ from those for cancer of the thoracic esophagus.

The management of carcinoma of the cervical esophagus is controversial. The choice of treatment has been surgical resection, radiation therapy, or combination of the two. Until recently, the treatment of carcinoma of the cervical esophagus has been dominated by surgical resection [2]. Surgery requires the removal of the esophagus, hypopharynx, and larynx, thus leaving the patient with a permanent tracheostomy. Recent developments in chemoradiation therapy have challenged the need for such extensive resections in the management of esophageal cancer, and the concept of organ preservation in patients with respectable carcinoma has been introduced with the aim of improving quality of life. However, relatively few patients treated with this combination have had carcinoma of the cervical esophagus [3].

We carried out this review to evaluate our own therapeutic results, and to serve as a future radiotherapy guideline.

Materials and methods

Between 1988 and 2002, 414 patients underwent radiotherapy for cancer of the esophagus at the Tenri Hospital. A total of 36 (8.7%) patients with a diagnosis of carcinoma of the cervical esophagus were treated with radiotherapy. Radiotherapy was

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performed before or after surgical resection in nine patients, and they were excluded from this study. Consequently, 27 patients with carcinoma of the cervical esophagus who were treated with definitive radiotherapy were enrolled in the study. Clinical staging was based on the categories of the International Union Against Cancer (UICC 1997). Staging procedures of T-factor included barium swallow, esophagoscopy, and computed tomography (CT) scan. To clarify the precise intramural spread of esophageal carcinoma, esophagoscopic biopsy was performed at several points with the guidance of the Lugol staining method. The extent of tumor invasion within the esophageal wall was evaluated by EUS whenever a probe could pass through stenosis of esophageal carcinoma. Bronchoscopy was performed if necessary. N-factor was determined by CT and/or endoscopic ultrasonography (EUS). A criterion for positive nodal involvement is >1.0 cm in the shortest transverse axis on CT. To exclude metastases elsewhere, we performed cervical and thoracoabdominal CT, ultrasonography of the cervical lesion. All patients were examined barium swallow, esophagoscopy and CT scan.

The initial tumor response was based on esophagoscopy and/or CT scans following completion of the treatment. Complete response (CR) was defined as the complete disappearance of all objective evidence. Partial response (PR) was defined as a 50% or greater decrease in the sum of the products of the diameters of measurable tumors. Stable disease (SD) was defined as a less than 50% decrease or a less than 25% increase. Progressive disease (PD) was defines a greater than 25% increase.

Local failure was defined as radiologic or endoscopic evidence of tumor regrowth in the cervical esophageal tumor and/or initially involved lymph nodes. Radiation-induced effects on normal tissues were assessed according to the criteria of the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 2.0.

Differences between pairs of groups in patient characteristics, response rates, and incidences of toxicity were evaluated by the χ^2 test. Survival and loco-regional control rates were calculated by the Kaplan-Meyer Method. The log-rank test was used for univariate analysis. Multivariate analysis was performed with Cox's proportional hazard model. All statistical analyses were performed using the computer program StatView for Windows Ver 5.0 (SAS Institute, Berkeley, CA, USA). The significance level was set at $p < 0.05$ and p values between 0.05 and 0.10 were considered to reveal a marginally significant influence.

Results

Patients' characteristics

Table I show the patient and tumor characteristics. The mean age of the study population was 64.8 years (range 51 to 82). Of the group, 22 (81%) were men and five (19%) were women. The performance status according to the ECOG scale was 0 or 1 in 19 cases, and 2 or 3 in eight cases.

Tumor characteristics

According to the TNM classification, seven patients were T1; one was T2; 12 were T3; and seven were T4. Primary tumor length ranged from 1.5 to 11 cm in diameter (mean, 5.9 cm). Fifteen patients (56%) had extension of the disease beyond the cervical esophagus. The site of direct extension was the upper region of the thoracic esophagus in 12 patients and hypopharynx in three patients. All patients had biopsy-proven squamous cell carcinoma.

Table I. Patient and tumor characteristics of 27 patients with cervical esophageal cancer.

Age (years)	
Range	51–82
Median	63
Sex	
Male	22
Female	5
Performance status	
0–1	19
2–4	8
Stage	
I	5
IIa	3
IIb	3
III	12
IV	4
Tumor length	
Range	1.5–11 cm
Mean	5.9
Tumor direct invasion	
To hypopharynx	3
To Ut (upper thoracic region)	12
Synchronous cancer	
Oropharynx	4
Hypopharynx	1
Mt (middle thoracic region)	2
Concurrent chemotherapy	
With	23
Without	4
Radiation dose	
<50 Gy	3
50 Gy$\leq$, <60 Gy	4
60 Gy$\leq$, <70 Gy	15
70Gy$\leq$	5

Lymph node metastasis was found in 17 patients (63%). Metastasis was confined to the cervical nodes in nine patients (33%) and to the upper mediastinal nodes in four patients (15%). Simultaneous metastasis to the cervical and mediastinal lymph nodes was observed in four patients (15%). Of the eight patients with mediastinal lymph node metastasis with or without cervical lymph node metastasis, five had primary tumors involving proximal parts of the thoracic esophagus.

Second malignancy

Five patients (19%) had been treated for a previous malignancy. The sites of previous malignancy were lung (2), stomach (1), tongue (1), and malignant lymphoma of neck (1). Concurrent malignancy was found in six patients (22%). All concurrent malignancies were detected by endoscopic inspection and early squamous cell carcinoma. The most common second primary site found was the oropharynx (3), followed by the mid-thoracic region of esophagus (2), and simultaneous of hypopharynx and oropharynx (1). One patient was found to have metachronous and concurrent malignancy. Overall, 33% of the patients had a synchronous or metachronous second malignancy.

Radiotherapy

A typical course of radiation therapy consisted of 40–50 Gy over 4–5 weeks using T-shaped anterior-posterior parallel opposed portals to include the primary lesion and the regional lymph nodes. The upper limit was the thyroid notch and the lower limit was 3–5 cm caudal of bronchial carina. The anterior-posterior portals were discontinued, paired anterior wedge fields or oblique opposed portals redesigned to exclude the spinal cord. Synchronous second tumor was included in the radiation fields. Fifteen patients received daily fractions of 2.2 Gy using bifractionation with a 6 hour interval, which is the same as our protocol for thoracic esophageal cancer [4]. The others received standard fractionation in daily fractions of 1.8–2.0 Gy. The total external radiation dose ranged from 44 to 73.7 Gy (mean 66). Three patients received <50 Gy because of medical problems during treatment periods. High-dose-rate intraluminal brachytherapy (HDRIBT) following external irradiation (8–10.5 Gy/2–3 fractions) at a level 5 mm below the surface of the mucosa was delivered in four patients. HDRIBT was performed by remote afterloading system with ^{60}Co source (RALSTRON-20B, Shimazu Co., Kyoto, Japan) or ^{192}Ir source (VarSource, Varian Co.). Twenty-three patients received concurrent chemotherapy of concomitant cisplatin and 5-fluorouracil (5FU) in the same way of our thoracic esophageal cancer protocol [4]. The regimen consisted of a large bolus of 50–80 mg/m^2 cisplatin given on Day 1 followed by four days infusion of 5FU (500–750 mg/m^2 daily). These consisted of three courses every three weeks of the same regimen. Chemotherapy could not be administered according to plan because of acute toxicities or the refusal of chemotherapy; therefore, the overall courses of chemotherapy were one course in five patients, two courses in eight patients and three courses in ten patients.

Response

CR was obtained in 13 patients, 11 had PR, three patients showed SD, and no patient had PD after irradiation. The response rate (CR+PR) was 89%.

Survival

At the time of analysis, the median follow-up period was 41 months, with a range of 16–123 months. At the time of this analysis (April 2004) 11 patients (41%) were still alive: four without evidence of disease and seven with recurrence. Sixteen patients died due to tumor progression. The actuarial overall survival rates at 1, 3 and 5 years were 55.6%, 37.9% and 37.9%, respectively, with a median survival of 13.9 months. The disease-free survival rates at 1, 3 and 5 years were 25.9%, 13.0% and 13.0%, respectively. The median disease-free survival time was 7.2 months. The overall and disease-free survival curves for all 27 patients are shown in Figure 1.

Failure pattern

Twenty-three patients (85%) experienced recurrence 3–38 months (median 6 months) after starting the

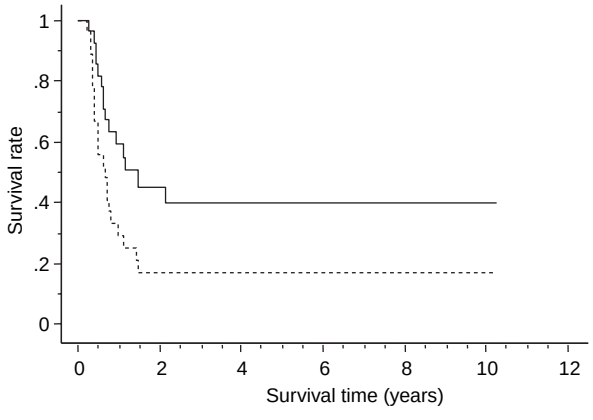

Figure 1. Survival curves of 27 patients with cervical esophageal cancer. Overall survival curve (solid line), disease-free survival curve (dotted line).

Table II. Acute and Late Toxicity.

Acute (1)	Grade 2	Grade 3	Grade 4/5	% Grade 3 ≤
Mucotitis/esophagitis	17	4	0	15%
Anemia	7	2	0	7%
Thrombocytopenia	1	2	0	7%
Leucopoenia	7	7	0	26%
Renal dysfunction	4	0	0	0%
Lung	1	0	0	0%
Late (2)				
Hypothyroidism	5	0	0	0%

(1): NCI-CTC ver.2, (2): RTOG/EORTC score.

therapy. Local recurrence was noted in 13 patients. All seven patients with less than 60 Gy had a local failure. Recurrence of distant lesion occurred in 11 patients. The sites of metastasis were lung (3), parapharyngeal lymph nodes (3), mediastinal lymph nodes (2), supraclavicular lymph nodes (2), liver (1), bone marrow dissemination (1) and region of lower-thoracic of esophagus (2). Parapharyngeal lymph node metastases were observed in two among three patients who had direct invasion to the hypopharynx.

Salvage therapy

Among the 11 patients with local recurrence, one patient was underwent salvaged therapy (ethanol injection). The two patients who had recurrence in the lower-thoracic of the esophagus underwent EMR. They were still alive at the time of this analysis.

Toxicity

Table II shows the associated acute and late toxicity. Grade 3 esophagitis (necessitating feeding tube or intravenous hyperalimination) occurred in four patients. Seven patients showed grade 3 leucopenia (white blood cells $<2\,000/mm^3$) and two patients showed grade 3 thrombocytopenia (platelets $<50\,000/mm^3$). Two patients showed grade 3 decreased of hemoglobin (6.5– <8.0 g/dl). Four patients showed grade 2 increases in serum creatinine level (<1.5–$3.0 \times$ normal). One patient, who had a past history of left upper lobe lobectomy due to lung cancer, developed Grade 2 radiation pneumonitis. Among the eight patients who survived over two years, five patients had hypothyroidism.

Prognostic factors

Table III shows the cause-specific survival rates and their associated p values as calculated by univariate and multivariate analyses of various factors possibly affecting prognosis. On univariate analysis, only two of the possible prognostic factors were found to actually influence survival: performance status ($p < 0.01$) and tumor length ($p < 0.01$).

Discussion

In the present study, there are some limitations. This is a retrospective, non-randomized study and enrolled cases are small and heterogeneous. One third of the patients had a synchronous or metachronous second malignancy, some bias might still remain. Although the cervical esophagus is anatomically distinct from the hypopharynx, the reported results of cancer treatments are often combine for these two sites. However, despite similar surgical management, treatment results differ for these two sites. There are a few reports on the surgical or radiation treatment outcome of only cervical esophageal cancer.

Triboulet et al. reported [5] the outcomes of surgical treatment for hypopharyngeal ($n = 131$) and cervical esophageal ($n = 78$) cancers. The median survival rate and 5-year survival rate were 21 months for hypopharyngeal cancer, and 14 months and 14% for cervical esophageal cancer, respectively. The prognosis of cervical esophageal cancer was

Table III. Cause-specific survival rates and p values calculated by univariate analyses.

Variable (condition)	n	1-year survival rate	3-year survival rate (%)	Univariate p
Age in years (65 >: 65 ≤)	15: 12	53: 55	38: 29	0.84
Performance status (0–1: 2–4)	19: 8	66: 25	45: 13	<0.01
Stage (I/II–IV)	5: 22	100: 50	75: 31	0.06
Tumor length (≤6 cm: >6 cm)	11: 16	80: 38	67: 15	<0.01
N factor (N0: N1)	10: 17	67: 46	33: 39	0.87

Table IV. Results of surgery for cervical esophageal cancer.

Series	year	No. of patients	Operative mortality	Survival rate	
				3-year	5-year
Kakegawa [1]	1985	64	11%	NA	27%
Nishimaki [6]	2002	32	13.5%*	33.8%*	31.2%*
Triboulet [5]	2001 (hypopharyngeal cases)	78 (131)	4.8%*	22% (36%)	14% (29%)

*with hypopharyngeal cases, NA: not available.

significantly worse than hypopharyngeal cancer ($p = 0.02$). The 5-year survival rate of these investigations was reportedly less than 30% [1,5,6] (Table IV). The operative mortality was 4.8% to 13.5%. On the other hand, Mendenhall et al. [7] reported the treatment results of 34 patients who had undergone radiation therapy alone (Table V). The 5-year survival rate was 17%, and local control rate was 26%. This is approximately equal to the operative results. Mendenhall concluded that high-dose radiation therapy should be used in an effort to improve the rate of local control.

Concomitant chemoradiation has been shown to be superior to radiotherapy alone in the management of thoracic esophageal cancer [3]. Stuschke et al. [8] and Burmeister et al. [9] investigated chemoradiation for cervical esophagus cancer. Stuschke reported a three-year survival rate of 24% in chemoradiation study of 17 patients. Burmeister reported on 34 patients with cervical esophageal cancer treated with chemoradiation consisting of CDDP and 5-FU. They reported 3- and 5-year survival rates of 58% and 55%, respectively. While their results were encouraging, there were no stage IV cases in their study, which may have led to these higher survival rates. Our results fell in between those of Mendenhall with radiation alone and Burmeister.

In this study, cases with a tumor size less than 6 cm diameter had a good prognosis. Especially, in patients with stage I, the 3-year and 5-year survival rates were 75% and 75%, respectively. The availability of chemotherapy combination was not clear, but there was acute disorder in tolerance level. It is thought that organ preservation is possible by definitive chemoradiation for early cancers.

It is well established that multiple cancers can occur in the upper aerodigestive tract of patients with squamous cell carcinoma of the head and neck [10]. This phenomenon has been explained by the concept of "field cancerization" proposed by Slaughter et al. [11], in which repeated exposure to carcinogens leads to an accumulation of genetic alterations, resulting ultimately in the development of multiple and independent cancers. In this study, there were six cases (22%) with concurrent head and neck squamous cell carcinoma. This phenomenon makes a definitive surgical therapy for cervical esophageal cancer difficult. We included concurrent head and neck tumors in the radiation field in this study. Lugol chromoendoscopy is essential for detection of concurrent early epithelial lesions to set the radiation fields.

For cancers in this region, it is especially difficult to plan treatment due to problems related to the complex shape of the target volume, lung inhomogenesities, changing contours, and the curved spinal cord. Treatment planning for carcinoma of the cervical esophagus represents a significant technical challenge [1]. The esophagus lies only 2 to 3 cm anterior to the spinal cord. Treatment planning includes consideration of the lower neck and upper thorax, which have dissimilar shapes and thicknesses, and ensuring that the esophagus does not present constant in relation to the skin surfaces. In addition, the lymph nodes at risk must be incorporated into irregular treatment volume. In this study, parapharyngeal lymph node metastases were

Table V. Results of radiation therapy for cervical esophageal cancer.

Series	year	No. of patients	Radiation dose (Gy)	Chemotherapy	Survival rate	
					3-year	5-year
Mendenhall [7]	1988	34	47–75 (mean 67.5)	None	34% (2-year)	17%
Stuschke [8]	1999	17	60–66	CDDP/5FU VP-16/Leucovorin	24%	NA
Burmeister [9]	2000	34	50.4 – 65 (mean 61.2)	CDDP/5FU	58%	55%
Current study	2005	27	44–73.7 (mean 66)	CDDP/5FU	38%	38%

NA: not available.

observed in two patients among three patients who had direct invasion to the hypopharynx. Of the eight patients with mediastinal lymph node metastases with or without cervical lymph node metastases, five had primary tumors involving proximal parts of the thoracic esophagus. Examination of techniques of three-dimensional radiotherapy [12] or intensity modulated radiation therapy is necessary to determine the large radiation field.

Due to the limitations of using a small number of subjects, additional studies including prospective ones, are needed to confirm the usefulness of chemoradiation.

Conclusion

This retrospective study showed that organ preservation is possible by definitive chemo-radiotherapy for early cervical esophageal cancers. In conclusion confirmative studies in large prospective trials are needed.

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