Efficacy of Concurrent Chemoradiotherapy for T1 and T2 Laryngeal Squamous Cell Carcinoma Regarding Organ Preservation

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Abstract. *Background: Although the survival rate of early-stage laryngeal squamous cell carcinoma (SCC) patients treated by radiotherapy (RT) is sufficient, the larynx preservation rate is unsatisfactory. To improve the larynx preservation rate, such patients have been treated by RT with chemotherapeutic agents. Patients and Methods: RT with or without uracil-tegafur (UFT) was performed for T1 cases, and UFT and carboplatin for T2 cases. Results: In T1 cases, 30 patients received RT and 16 patients received concurrent chemoradiotherapy (CCRT). In T2 cases, 28 patients received RT and 45 patients received CCRT. There were no significant differences in the response and survival rates between the treatment methods both in T1 and T2 cases. The 5-year larynx preservation survival rate was improved significantly by CCRT in T2 cases (66.7% vs. 93.3%; p<0.01). Conclusion: CCRT for early-stage laryngeal SCC patients was efficacious to improve the larynx preservation survival rate.*

Radiotherapy (RT) is the most widely used definitive treatment for early-stage laryngeal squamous cell carcinoma (SCC) patients. The 5-year disease-specific survival rates with RT alone for T1N0M0 glottic type laryngeal SCC range from 94 to 98% and for T2N0M0 from 90 to 95% (1-4). The 5-year local control rates with RT alone for T1 glottic type laryngeal SCC range from 81 to 94% and for T2 from 18 to 80% (1-7). The surgical salvage rate after RT failure in T1 and T2 SCC of the glottic larynx ranges from 50 to 80% (8), and the 5-year larynx preservation survival rates with RT alone for T1 glottic type laryngeal SCC are 95% and range from 45 to 82% for T2 (4, 7). The purposes of treatment for laryngeal carcinoma are not only cure but also larynx preservation. To preserve the larynx, the definitive treatment by RT alone is thought to be inadequate for early-stage laryngeal SCC, especially for T2N0 cases. LASER surgery and partial laryngectomy are considered as alternative definitive treatment or salvage treatment for early-stage laryngeal SCC (9-15). However, both LASER surgery and partial laryngectomy have been reported as a result of poor voice quality (16-19). To improve the local control rate with definitive RT and to minimize the necessity for salvage surgery without decreasing the survival rate, uracil-tegafur (UFT) was administered for T1 laryngeal SCC patients, and both carboplatin (CBDCA) and UFT for T2 patients concurrently with RT. The results of treatment response, survival rate and the larynx preservation survival rate of concurrent chemoradiotherapy (CCRT) for early-stage laryngeal SCC patients are presented here and are compared to those of RT alone.

Patients and Methods

Eligibility criteria included the following: untreated stage I and II patients with squamous cell carcinoma of the larynx; TNM disease according to the 2002 staging classification system of the Union International Contre le Cancer (UICC) without other active carcinomas, the staging evaluated by endoscope, computed tomography (CT) scan, magnetic resonance imaging (MRI) and ultrasonographic (US) findings of the neck; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1; life expectancy > 3 months.

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From September 1991 until October 1997, patients had received radiotherapy (RT) alone. Since November, 1997 until now, CCRT with UFT for T1 cases, and with CBDCA and UFT for T2 cases has been applied. The UFT was administrated in a daily oral dose of 300 mg as tegafur, and CBDCA was administrated intravenously once a week within one hour prior to RT and six to seven times during RT. The weekly CBDCA dose was determined by the area under the curve (AUC), *i.e.*, 1.25 per week.

RT was given 5 days a week using a single daily fraction of 2.0 Gray (Gy) with 6 MV X-ray linear accelerators. The standard RT was given for the parallel opposed bilateral field, focusing the primary tumor for a total dose of 66-72 Gy.

At 4 to 6 weeks after the end of RT or CCRT, the clinical response was assessed for each patient according to the combined findings of fiberscope, CT scanning or MRI and ultrasonography. A complete response (CR) was defined as a complete disappearance of all measurable lesions for at least 4 weeks. A partial response (PR) was defined as a 50% or greater decrease in the product of two perpendicular diameters of each and all measurable lesions for at least 4 weeks. The patients in whom the disease did not fulfill the criteria for PR were considered as having no change (NC) or a stable disease. The pathological responses to the RT or CCRT were confirmed by biopsy at the primary site in all the patients. The patients with less than CR of the primary and newly diagnosed neck lymph node metastasis (evaluated by histopathological examinations) were under consideration for a planned surgery 6-8 weeks after the end of the RT or CCRT.

The disease-specific survival rate and the organ preservation survival rate were calculated by the Kaplan-Meier method and were statistically analyzed by the Wilcoxon test.

Toxicity was assessed during the treatment and 4 weeks after treatment using the 1998 National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0.

Results

Between July 1991 and May 2008, 288 previously non-treated laryngeal carcinoma patients had visited the institute and all cases were pathologically diagnosed as having SCC. Fifty patients had T1N0M0 and 86 patients had T2N0M0 in the TNM stages. Forty-six out of the 50 patients of T1, and 73 of the 86 patients of T2 were eligible for the present study. One hundred and fourteen patients were male and five female, the average age being 63.9 years (range 43-86 years). Patients' characteristics are summarized in Table I. The median follow-up time was 81.5 months (range 10-192 months). One patient died of an uncontrolled primary site tumor 10 months after the treatment and another 118 patients could be followed for more than 12 months.

Table I. *Patients characteristics.*

T1

	Overall (n=46)	RT (n=30)	CCRT (n=16)
Age (years)			
Average	64.6	66.8	60.5
Range	46-79	48-79	46-73
Gender (n)			
Male	42	28	14
Female	4	2	2
Site (n)			
Glottic	46	29	16
Supraglottic	0	0	0
Subglottic	1	1	0
Pathological differentiation (n)			
Poorly	5	4	1
Moderately	29	19	10
Well	12	7	5

T2

	Overall (n=73)	RT (n=28)	CCRT (n=45)
Age (years)			
Average	63.5	64.1	63.2
Range	43-86	48-86	43-84
Gender (n)			
Male	72	27	45
Female	1	1	0
Site (n)			
Glottic	62	25	37
Supraglottic	5	1	4
Subglottic	6	2	4
Pathological differentiation (n)			
Poorly	7	5	2
Moderately	44	13	31
Well	22	10	12

The degrees of toxicity are listed in Table II and there is no obvious difference between the treatment methods. The toxicities were all tolerable and no fatal case was observed.

The pathological complete response rate and recurrent sites of pathological CR cases are summarized in Table III. In the T1 cases, 45 out of 46 patients (97.8%) showed pathological CR at the primary site. The recurrence rate at the primary site was 24.4% (11 out of 45 CR patients) and that of lymph nodes in the neck was 2.2% (1 of 45 CR patients). In the RT group, all patients showed pathological CR at the primary site. The recurrence rate at the primary site was 33.3% (10 out of 30 CR patients) and that of lymph nodes in the neck was 3.3% (1 of 30 CR patients). In the CCRT group, 15 out of 16 patients (93.8%) showed pathological CR at the primary site. The recurrence rate at the primary site was 6.7% (1 out of 15 CR patients) and that of lymph nodes in the neck was 0% (0 of 15 CR patients). In the T2 cases, 67 out of 73 patients (91.8%) showed pathological CR at the primary site. The recurrence rate at the primary site was 22.4% (15 out of 67 CR patients) and that of lymph nodes in the neck was 3.0% (2 of 67 CR patients). In the RT group, 27 out of 28 patients (96.4%) showed pathological CR at the primary site. The recurrence rate at the primary site was 37.0% (10 out of

Table II. *Toxicity degrees.*

a. T1-RT (n=30)

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3
Hematological				
Anemia	26 (86.7%)	4 (13.3%)	0	0
Neutropenia	29 (96.7%)	1 (3.3%)	0	0
Thrombocytopenia	27 (90.0%)	3 (10.0%)	0	0
Non-hematological				
Diarrhea	30 (100%)	0	0	0
Fever	30 (100%)	0	0	0
Hepatic				
AST	25 (83.3%)	5 (16.7%)	0	0
ALT	27 (90.0%)	3 (10.0%)	0	0
Renal (Creatinine)	29 (96.7%)	1 (3.3%)	0	0
Related to radiation				
Dermatitis	16 (53.3%)	9 (30.0%)	3 (10.0%)	2 (6.7%)
Dysphagia	26 (86.7%)	3 (10.0)	1 (3.3%)	0
Mucositis	8 (26.7%)	15 (50.0%)	7 (23.3%)	0
Pain	18 (60.0%)	9 (30.0%)	3 (10.0%)	0

b. T1-CCRT (n=16)

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3
Hematological				
Anemia	9 (56.3%)	7 (43.7%)	0	0
Neutropenia	15 (93.8%)	0	0	1 (6.2%)
Thrombocytopenia	15 (93.8%)	1 (6.2%)	0	0
Non-hematological				
Diarrhea	16 (100%)	0	0	0
Fever	15 (93.8%)	1 (6.2%)	0	0
Hepatic				
AST	13 (81.3%)	3 (18.7%)	0	0
ALT	14 (87.5%)	2 (12.5%)	0	0
Renal (Creatinine)	16 (100%)	0	0	0
Related to radiation				
Dermatitis	5 (31.3%)	3 (18.8%)	6 (37.5%)	2 (12.4%)
Dysphagia	12 (75.0%)	3 (18.8%)	1 (6.2%)	0
Mucositis	0	6 (37.5%)	9 (56.3%)	1 (6.2%)
Pain	5 (31.3%)	8 (50.0%)	3 (18.7%)	0

c. T2-RT (n=28)

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3
Hematological				
Anemia	16 (57.1%)	12 (42.9%)	0	0
Neutropenia	27 (96.4%)	1 (3.6%)	0	0
Thrombocytopenia	27 (96.4%)	1 (3.6%)	0	0
Non-hematological				
Diarrhea	28 (100%)	0	0	0
Fever	28 (100%)	0	0	0
Hepatic				
AST	19 (67.9%)	9 (32.1%)	0	0
ALT	19 (67.9%)	9 (32.1%)	0	0
Renal (Creatinine)	26 (92.9%)	2 (7.1%)	0	0
Related to radiation				
Dermatitis	10 (35.7%)	12 (42.9%)	5 (17.9%)	1 (3.5%)
Dysphagia	22 (78.6%)	2 (7.1%)	4 (14.3%)	0
Mucositis	2 (7.1%)	21 (75.0%)	5 (17.9%)	0
Pain	16 (57.1%)	9 (32.1%)	3 (10.8%)	0

d. T2-CCRT (n=45)

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3
Hematological				
Anemia	23 (51.1%)	21 (46.7%)	1 (2.2%)	0
Neutropenia	41 (91.2%)	1 (2.2%)	2 (4.4%)	1 (2.2%)
Thrombocytopenia	30 (66.7%)	15 (33.3%)	0	0
Non-hematological				
Diarrhea	44 (97.8%)	1 (2.2%)	0	0
Fever	44 (97.8%)	1 (2.2%)	0	0
Hepatic				
AST	27 (60.0%)	18 (40.0%)	0	0
ALT	33 (73.3%)	12 (26.7%)	0	0
Renal (Creatinine)	37 (82.2%)	8 (17.8%)	0	0
Related to radiation				
Dermatitis	12 (26.7%)	19 (42.2%)	6 (13.3%)	8 (17.8%)
Dysphagia	27 (60.0%)	10 (22.2%)	8 (17.8%)	0
Mucositis	2 (4.4%)	30 (66.7%)	13 (28.9%)	0
Pain	19 (42.2%)	18 (40.0%)	7 (15.6%)	1 (2.2%)

27 CR patients) and that of lymph nodes in the neck was 3.7% (1 of 27 CR patients). In the CCRT group, 40 out of 45 patients (88.9%) showed pathological CR at the primary site. The recurrence rate at the primary site was 12.5% (5 out of 40 CR patients) and that of lymph nodes in the neck was 2.5% (1 of 40 CR patients). Salvage surgery of the primary site was performed for 11 patients of T1 cases, *i.e.*, 9 in the RT group (7 for total laryngectomy [TL] and 2 for LASER vaporization [LASER]), 2 in the CCRT (1 for TL and 1 for LASER), and 20 patients of T2 cases, *i.e.*, 11 in the RT group (9 for TL and 2 for LASER), 9 in the CCRT (4 for TL and 5

Table III. *Pathological complete response rates and recurrent sites of pathological CR cases.*

	Pathological		Recurrent sites of CR cases	
	CR	non-CR	Primary	LN
T1				
Overall (n=46)	97.8 (n=45)	2.2 (n=1)	24.4 (11/45)	2.2 (1/45)
RT (n=30)	100 (n=30)	0 (n=0)	33.3 (10/30)	3.3 (1/30)
CCRT (n=16)	93.8 (n=15)	6.2 (n=1)	6.7 (1/15)	0 (0/15)
T2				
Overall (n=73)	91.8 (n=67)	8.2 (n=6)	22.4 (15/67)	3.0 (2/67)
RT (n=28)	96.4 (n=27)	3.6 (n=1)	37.0 (10/27)	3.7 (1/27)
CCRT (n=45)	88.9 (n=40)	11.1 (n=5)	12.5 (5/40)	2.5 (1/40)

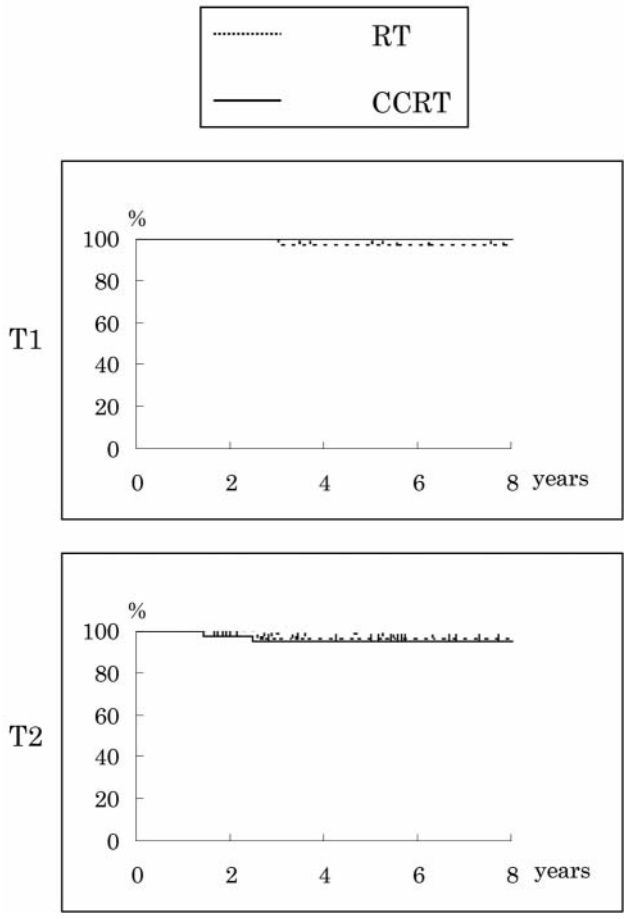

Figure 1. *The 5-year disease-specific survival rates of T1 and T2 cases were shown, in terms of the treatment modality.*

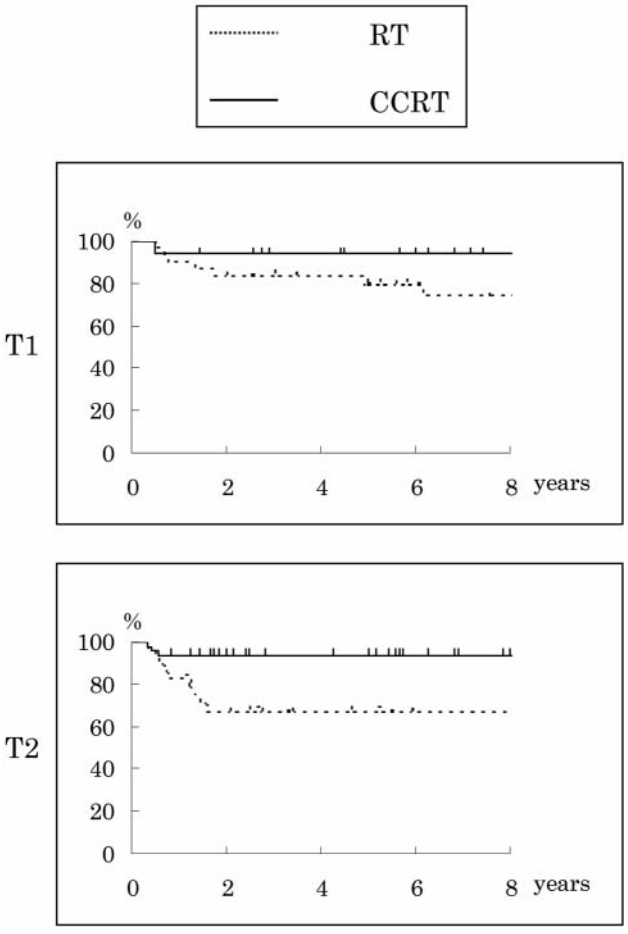

Figure 2. *The 5-year organ preservation survival rates of T1 and T2 cases were shown, in terms of the treatment modality.*

for LASER). The 5-year disease-specific survival rate was 98.0% in all of T1 patients, 96.0% in RT group and 100% in CCRT group (not significant; ns) (Figure 1). The 5-year organ preservation survival rate was 84.2% in all T1 cases, 79.4% in the RT group and 93.8% in the CCRT group (ns) (Figure 2). The 5-year disease-specific survival rate was 95.3% in all of T2 patients, 96.0% in RT group and 95.0% in CCRT group (ns) (Figure 1). The 5-year organ preservation survival rates were 83.2% in all T2 cases, 66.7% in the RT group and 93.3% in the CCRT group ($p<0.01$), respectively (Figure 2).

Discussion

Head and neck SCC (HNSCC) is found in 5% of all newly diagnosed cancers out of 400,000 new cases every year. Most of the patients with HNSCC are diagnosed at the advanced-stage (stage III and IV) on their first visit, whereas about half of laryngeal carcinoma patients are diagnosed at the early-stage (stage I and II). Contrary to other head and neck organs, *e.g.*, the pharynx, oral cavity, nasal cavity and para-nasal sinuses, the larynx especially the vocal cord, dysfunctions easily even with a minimum invasion. Therefore hoarseness appears as a first symptom in the glottic type laryngeal carcinoma. The early-stage HNSCC, including laryngeal carcinoma, is potentially curable by surgery and/or RT. The goals of treatment for laryngeal carcinoma are not only cure but also larynx preservation. Regarding to the larynx preservation, the definitive treatment by RT alone is considered as inadequate for early-stage laryngeal SCC, especially for T2N0M0 cases. LASER surgery and partial laryngectomy have been described as alternative definitive treatment or salvage treatment for early-stage laryngeal SCC (9-15). However, both treatment methods have been reported as a result of poor voice quality (16-19).

To improve the local control rate with definitive RT and to minimize the necessity for salvage surgery without decreasing the survival rate, UFT and CBDCA during the RT were administrated. UFT is an oral fluoropyrimidine with

pharmacokinetic properties resembling those of a 5-fluorouracil (5-FU) continuous infusion with the advantage of oral administration. The radiosensitizing efficacy of 5-FU strongly depends on continuous exposure to tumor cells and daily UFT administration is sufficient to maintain the circulating blood concentration of 5-FU (20, 21). CBDCA at a high dose has been found to be active in SCC (22, 23) and to have radiation-sensitizing properties similar to cisplatin (24) but with less nephrotoxicity (25). Considering the disease stage and the treatment compliance, UFT was administrated for T1 laryngeal SCC patients, and both CBDCA and UFT for T2 patients concurrently with RT. The toxicity and the efficacy of the regimen consisting of CBDCA and UFT were assessed and it was confirmed as a safe and efficacious treatment method (26, 27). There have been several reports in terms of the parameters that may influence the local control with RT for laryngeal SCC patients, *e.g.*, tumor extent, histological differentiation of SCC and pre-treatment hemoglobin (3, 6, 28-30). T stage is a good predictor for the local control rate after RT, and impaired vocal cord mobility and anterior commissure involvement are also considered as predictive factors for local control by RT. Histological differentiation of SCC has been reported to influence the local control and disease specific survival after RT by multivariate analyses. Poorly differentiated SCC indicated better results by RT. Furthermore, it has been reported that a lower pre-treatment hemoglobin level (*i.e.* <12 or 13 g/dl) is a poor prognostic factor for the local control in early-stage laryngeal SCC treated with RT (6, 29). In the present study, there was no severe anemia due to the adverse effect of CCRT compared with RT alone, and it was thought to not affect the prognosis. In fact, there was as improved 5-year organ preservation survival rate both in T1N0M0 and T2N0M0 laryngeal SCC patients treated by CCRT than that of RT alone, without decreasing the disease specific survival rate.

It can be concluded that CCRT utilizing UFT for stage I laryngeal SCC patients and both UFT and CBDCA for stage II patients is a safe and effective treatment allowing larynx preservation and minimizing the necessity for salvage surgery without decreasing the survival rate. The chemotherapy regimen is well tolerable without severe adverse effects and it can be performed at an outpatient clinic or with short hospitalization. Therefore the present CCRT regimen can be considered as one of the treatment methods for early-stage laryngeal SCC patients.

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