Concurrent chemoradiotherapy with docetaxel for T2 laryngeal carcinoma

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Objective: To evaluate the efficacy and safety of concurrent chemoradiotherapy with docetaxel (DOC) for T2 laryngeal carcinoma.
Method: Twelve patients with T2 laryngeal cancer received concurrent chemoradiotherapy (60-70Gy) with weekly DOC (10 mg/m²) (CCRT group). The clinical files of the patients were retrospectively reviewed and survival rates and laryngeal preservation rates were analyzed compared with the group treated with conventional radiation therapy alone (RT group).
Results: Complete response was observed in 11 of 12 patients (91.7%) in the CCRT group. Overall 5-year survival rates by Kaplan-Meier's method were 90% for the CCRT group and 78% for the RT group. The disease free survival with anterior commisure involvement was 90% in CCRT group and 53% in RT group, respectively. Toxicity over grade III was noticed in 3 patients.
Conclusion: Concurrent chemoradiotherapy with DOC is a feasible and effective treatment modality for organ preservation in T2 laryngeal cancer in the outpatient setting. Efficacy and safety of this treatment modality in an outpatient setting were discussed.

Key words: laryngeal preservation, outpatient, chemotherapy, radiotherapy

INTRODUCTION

Early laryngeal cancer is a highly curable disease showing excellent local control rates by either radiotherapy or surgery [1, 2]. Generally, radiation therapy is chosen as the initial treatment in Japan, for early-stage laryngeal cancers other than the well-defined T1a glottic cancer, which is transorally excised by laser surgery. T1 cases respond to radiation therapy very well and high laryngeal preservation rate is obtained. T2 laryngeal cancer also has a good prognosis with good response to radiation therapy. However, local control rate for T2 laryngeal cancers has been reported to be 60-70% [2-6]. Some T2 cases are radio-resistant and surgical treatment including partial or total laryngectomy is required for residual or relapsed tumor. Although the decision of radio-sensitivity before treatment is very important, there are few reports concerning the definitive prediction of radio sensitivity [1]. To improve local control, accelerated hyperfractionation [7] or a radio-sensitizer with anti-cancer drugs [8] has been introduced for treatment.

Various anti-cancer drugs have been used as combination drugs with radiation. Docetaxel (DOC) is a novel semisynthetic agent of the taxoid class that acts by enhancing tubulin polymerization and inhibiting microtubule depolymerization [9]. DOC was reported to show a high response rate in advanced head and neck cancer [10, 11]. Fujii et al. [12] proposed the concomitant administration of weekly DOC with radiotherapy for head and neck cancer. Since 2002 we have treated a limited group of stage II laryngeal cancer patients by concurrent chemoradiotherapy with DOC to improve local control. We retrospectively evaluated the results of the treatment and discuss the efficacy for organ preservation and safety in the outpatient setting.

Patients and Methods

Forty-two patients with T2N0 laryngeal cancer who were treated by RT between 2002 and 2006 were retrospectively analyzed. All of the 42 cases had been diagnosed to have squamous cell carcinoma. They were divided in to two groups as follows.

Concurrent chemoradiotherapy (CCRT) with DOC group (CCRT group)

The subjects were 12 stage II (T2N0M0) laryngeal cancer patients treated concurrently with radiotherapy and DOC (CCRT group). TNM category was determined by 1997 UICC TNM classification. The criteria of the indication were confined to primary lesions with impaired vocal code mobility, tumor bulk, and anterior commissure invasion, predicted to be radio-resistant with conventional radiotherapy alone. All patients had a performance status of 0 or 1 and with normal liver, kidneys and bone marrow functions by laboratory examination. The observation period for the patients ranged from 20 to 72 months with a mean of 44 months. The characteristics of the patients are summarized in Table 1.

All patients received radiation for the primary lesion with 2.0 Gy single daily fractions, 5 times a week for a total dose of from 60 to 70 Gy. DOC (10 mg/m²) was administered intravenously for 1 hour once a week for

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Table 1 Characteristics of the patients with concurrent chemoradiotherapy (CCRT group) and those with radiotherapy alone (RT group)

		CCRT	RT
All cases		12	30
Sex	Male	11	29
	Female	1	1
Mean Age		68	65
Subsite	Supraglottis	4	7
	Glottis	7	21
	Subglottis	1	2
Anterior commisure involvement			
	Positive	10	17
	Negative	2	13

Table 2 Clinical responses and relapse (salvage surgery) with CCRT group and those with RT group.

		CCRT	RT
		12	30
Clinical responses	CR	11	30
	PR	1	0
	NC	0	0
	PD	0	0
Local relapse		1	7
Transoral laser surgery		0	1
Total laryngectomy		1	5
No surgery		1	1

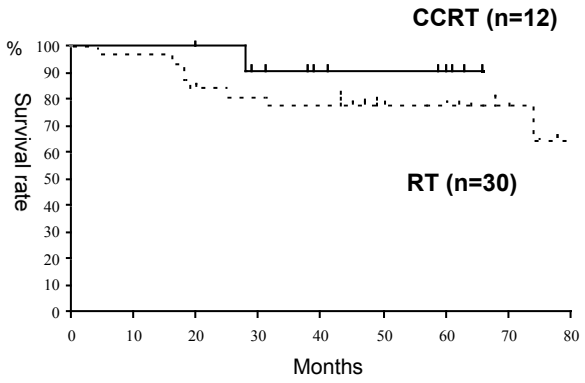

Fig. 1. Overall survival rates of the CCRT group (solid line) and RT group (dotted line) by Kaplan-Meier's method.

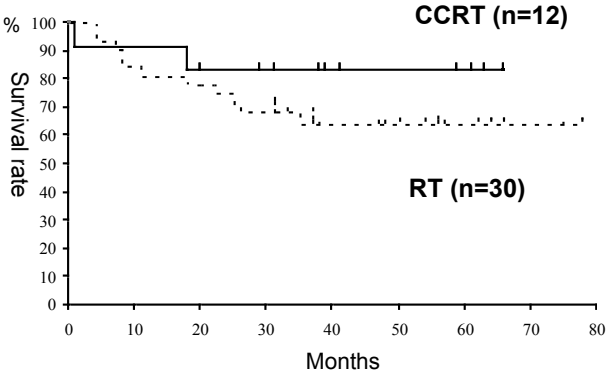

Fig. 2. Disease free survival rates of the CCRT group (solid line) and RT group (dotted line) by Kaplan-Meier's method.

6 consecutive weeks concurrently with radiotherapy. Patients were treated as outpatients except 2 cases who were admitted to the hospital during treatment for family reasons. The written informed consent was obtained from all patients before the treatment.

Conventional radiotherapy alone group (RT group)

Thirty stage II (T2N0M0) laryngeal cancer (squamous cell carcinoma) patients treated by radiotherapy alone were evaluated as the control group (RT Group). Patients received radiation of 2.0 Gy single daily fractions, 5 times a week for a total dose of from 60 to 70 Gy. The follow-up period ranged from 4 to 69 months with a mean of 42 months.

Complete response (CR) was defined as complete clinical disappearance of the primary tumor. A partial response (PR) was characterized as a reduction by at least 50% of the tumor volume. The response was evaluated by the fiberscopic findings one month after the completion of the irradiation [12], because the T2 laryngeal tumors are usually non-measurable lesions by the CT or MRI images. Cumulative survival rates and laryngeal preservation rates were calculated by Kaplan-Meier's method. Comparison of the two groups was analyzed by the log-rank test. Stat-Mate ver. III (ATMS, Tokyo Japan) was used for the statistical evaluations. The toxicities were graded according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) (2003).

RESULTS

The planned 6-cycle administration of DOC could be conducted in all cases. CR was obtained in 11 cases and PR in one case in the CCRT group. One PR case underwent total laryngectomy two months after the radiotherapy for salvage. All 30 cases in RT group achieved CR (Table 2).

Local relapse occurred in two CCRT group patients 6 and 19 months after radiotherapy respectively. One patient underwent a total laryngectomy and lives without disease. Another patient rejected salvage surgery and died of local disease. In the RT group 7 of 30 cases had local relapse. One case underwent laser cordectomy while 5 cases underwent total laryngectomy for salvage operation (Table 2). Another one patient rejected salvage surgery.

The overall 5-year survival rates were 90% for the CCRT group and 78% for the RT group (Figure 1). Disease free 5-year survival rates were 82% and 63%, respectively (Figure 2). Both of the above showed no significant statistical difference by log-rank test ($p=0.44$ and $p=0.26$, respectively). The overall laryngeal preservation rates were 82% in the CCRT group and 78% in the RT group. Laryngeal preservation rates

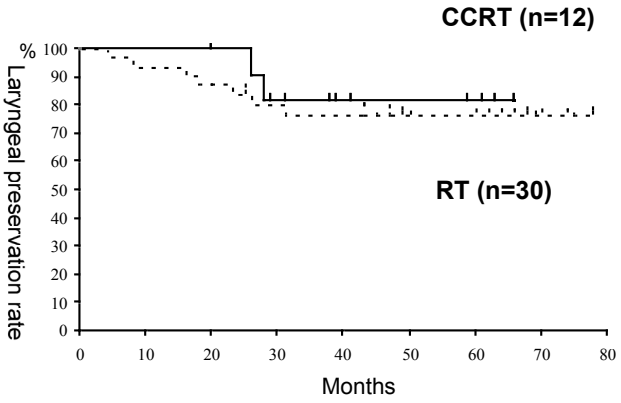

Fig. 3. Laryngeal preservation rates of the CCRT group (solid line) and RT group (dotted line) by Kaplan-Meier's method.

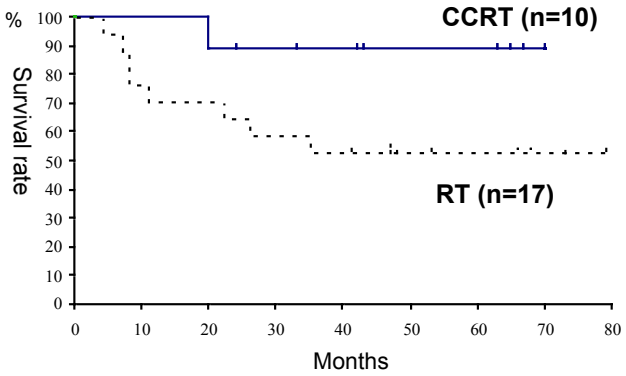

Fig. 4. Disease free survival rates of the anterior commisure involved cases in CCRT group (solid line) and RT group (dotted line). There was no statistical difference by log-rank test.

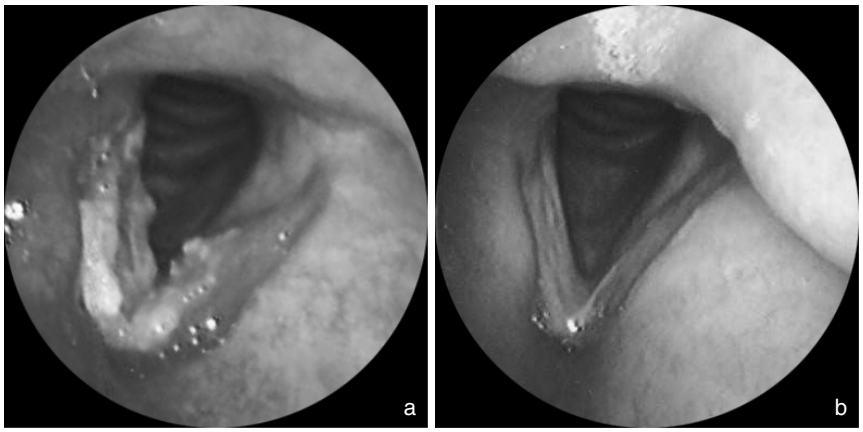

Fig. 5. The representative case of CCRT group.
a: The tumor was originated from the right vocal cord involving the anterior commisure before treatment.
b: The tumor disappeared after 70 Gy of concurrent chemoradiotherapy with DOC .

Table 3 Toxicity in the CCRT group patients according to CTCAE v 3.0

Grade	1	2	3	4
Mucositis	6	5	1	0
Dermatitis	5	6	1	0
Leukopenia	2	0	0	0
Lymphopenia	1	1	2	0
Hemoglobin	1	0	0	0
Platelet	1	0	0	0

of supraglottic, glottic, subglottic cancers in the CCRT group were 100% (4/4), 86% (6/7), and 0% (0/1), respectively. Meanwhile the corresponding laryngeal preservation rates in the RT group were 43% (3/7), 90% (19/21), and 50% (1/2), respectively. The cases with anterior commisure involvement were 10 in CCRT group and 17 in RT group (Table 1). The disease free survival with anterior commisure involvement was 90% in CCRT group and 53% in RT group, respectively (Figure 4). However, no significant statistical difference was observed by log-rank test (p=0.69). The representative case of CCRT group was demonstrated. The tumor from the right vocal cord involving the anterior commisure (Figure 5a) disappeared after 70 Gy of concurrent chemoradiotherapy with DOC (Figure 5b).

Adverse events over grade III were noticed in three patients (Table 3). One case developed grade III dermatitis and mucositis after 4 cycles of administration, who abandoned DOC followed by scheduled radiation therapy alone. The others had grade III lymphopenia but completed the scheduled concurrent chemoradiotherapy without interruption.

DISCUSSION

Functional preservation is a matter of importance in the treatment of early laryngeal cancers as well as local control. The initial treatment modality for early laryngeal cancers includes radiation and conservative surgery [1]. The preferred treatment modality is highly dependent on geography for early laryngeal cancers [1]. Radiotherapy is the treatment of choice in north-

ern Europe, whereas patients are more likely to be treated with surgery in the United States and southern Europe [1]. In Japan conventional radiotherapy is the treatment of choice for stage II laryngeal cancers in general.

The 5-year local control rates of T2 glotttic and supraglottic laryngeal cancers by conventional radiotherapy were reported as 63–76% and 59–83%, respectively [2–6]. Supraglottic cancers tend to have a poor local control rate. To improve local control radiation therapy is modified, such as by adding an accelerated fraction [7, 13] and the concurrent administration of a radio-sensitizer [8]. For advanced laryngeal cancers, neo-adjuvant chemotherapy has been reported to be effective in preserving the larynx without compromising overall survival [14]. Recently, concurrent chemoradiotherapy with cisplatin has been reported to be superior to induction chemotherapy followed by radiotherapy or radiotherapy alone for laryngeal preservation and locoregional control [15]; therefore, we applied concurrent chemoradiotherapy for stage II laryngeal cancer and evaluated the efficacy and safety of the treatment modality. The discussion focused on local control and the feasibility in an outpatient setting.

Various chemotherapeutic agents including cisplatin have been used for concurrent chemoradiotherapy of head and neck cancer. DOC is one of the most promising new agents for combination with radiation. Previously Fujii et al. reported phase I/II trials of weekly DOC and concomitant radiotherapy for head and neck cancer [12]. They concluded that low-dose DOC showed a strong effect in combination with radiation, with a high survival rate in CR patients. In the phase I study the recommended dose of weekly DOC administration was determined as 10 mg/m^2. As we participated in this study [12], we followed this dosage for concurrent chemoradiotherapy for early laryngeal patients.

In a randomized trial (RTOG 91–11) [15] the authors stated that in most laryngeal cancer, the disease can be managed without a primary surgical approach; however, Weinstein et al. argued that a significant number of advanced laryngeal cancers are candidates for organ-preserving surgical techniques [16]. For T2 invasive glottic cancers, Laccourreye reported the efficacy of platinum-based induction chemotherapy and partial laryngeal surgery [17]. This multimodal treatment strategy achieved 95.7% 5-year local control rate. In Japan radiation therapy is the treatment of choice for T2 laryngeal cancers in general; however, some T2 cases do not respond to radiation therapy very well.

The prediction of local control by radiotherapy is very important for the indication of the treatment modality. Various prognostic factors affecting local control have been reported including T stage, anterior commissure involvement, tumor bulk, fraction size, field size, and overall treatment time for early laryngeal cancers [18, 19]. More recently, radiological examination including tumor volume by CT has become a significant predictor [6, 20]; however, there is no definitive predictive factor, so far. The prognostic significance of cancer-associated membranous protein or oncogene, such as epidermal growth factor receptor and Cyclin D1 in laryngeal cancer treated with radiation has been proposed [21, 22]. Selection criteria for radiation or surgery as a primary treatment could be established in the near future by these molecular or immunohistochemical analyses.

In Japan, continuous infusion of anti-cancer drugs such as cisplatin and 5-fluorouracil usually requires hospitalization. In our cases treated with concurrent administration of DOC, two cases had grade III adverse events of lymphopeia who underwent the scheduled treatment. Only one patient abandoned DOC after 4 cycles of administration because of grade III dermatitis and mucositis; however, this patient received radiation alone thereafter without hospitalization. This treatment modality is safe and feasible in the outpatient setting.

As this study was not designed as a randomized control study, the selection criteria for CCRT were confined to a primary lesion, predicted to be less sensitive to conventional radiotherapy alone, so there is a selection bias between CCRT and RT groups. Although the CCRT group was estimated to be less sensitive to radiotherapy, the local control rates and survival rates were similar to that of the RT group. And the ratio of supraglottic cancer to glottic cancer in the CCRT group (2 : 3) was higher than that in the RT group (1 : 3) which also affected the results. In fact the laryngeal preservation rates of the supraglottic cancers in the CCRT group are better than that in the RT group in our study (100% vs 43%).

Because the cases with anterior commisure involvement tend to be radio-resistant [18, 19], we analyzed the cases with the anterior commisure invasion. The disease free survival rate of the anterior commisure involved cases were compared between CCRT and RT groups. The disease free survival of CCRT group (89%) was higher than that of RT group (52%). Although the statistical difference was not observed, CCRT with DOC might be an effective radio-sensitizer for the T2 laryngeal cancer with anterior commisure involvement.

All of the facts above suggest that the concurrent chemoradiotherapy has preponderance for the control of the cancer from supraglottic origin and that of anterior commissure involvement over the conventional radiotherapy. No survival benefit or improvement of local control was demonstrated statistically in this study because of the limited number of cases and selection bias; however, CCRT with DOC is a feasible and effective treatment modality for organ preservation of laryngeal cancer in the outpatient setting. This would be a good indication especially for the selected cases such as anterior commissure involvement.

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