

Effectiveness of Chemoradiotherapy for T1b-T2 Glottic Carcinoma

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Abstract

Local control rates for T1b-T2 glottic carcinoma are not satisfactory. The purpose of this study was to evaluate the outcomes of patients with T1-T2 glottic carcinoma treated with radiotherapy and to evaluate the effects of chemoradiotherapy for T1b and T2 disease. At Hiroshima City Asa Citizens Hospital, 49 patients with early glottic carcinoma underwent radiotherapy from July 2006 to December 2015. Of these, 46 patients were enrolled and evaluated. The median age was 70.5 years (range, 39-88 years), and 43 patients (93.5%) were men and 3 patients (6.5%) were women. All patients presented with squamous cell carcinoma. Twenty-eight (60.1%) had T1a, 6 (13%) had T1b and 12 (26.1%) had T2 disease. In T1 and T2 patients, 2 Gy/fraction was used and the total prescribed dose ranged from 60 to 66 Gy and from 60 to 70 Gy, respectively. The patients with T1b and T2 were administered chemotherapy. The patients with T1 disease had a 5-year local control rate of 90.9%, while patients with T2 disease had a local control rate of 80.0%. The patients with T1a disease had a 5-year local control rate of 88.9%, while patients with T1b disease had a local control rate of 100%. Chemoradiotherapy for patients with T1b-T2 glottic carcinoma is feasible and may contribute to improved local control of patients with T1b disease.

Keywords: Glottic carcinoma; Radiotherapy; Chemoradiotherapy; Local control

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Introduction

Glottic cancer is the most common laryngeal cancer. Patients with T1-T2N0 squamous cell carcinoma of the glottic larynx may be treated with transoral laser excision, open partial laryngectomy, or radiotherapy [1]. Radiotherapy for early glottic carcinoma results in good clinical outcome and can preserve the structure and function of the larynx. Many studies showing the effectiveness of radiotherapy for glottic carcinoma have been reported. It is important to continue to confirm the effectiveness of this treatment in the future.

For T1 glottic carcinoma, the 5-year local control rate has been reported to be approximately 80-90%, whereas for T2 glottic carcinoma, the local control rate is 70-80% [1-6]. In T1 disease, T1b glottic carcinoma tends to have a lower local control rate of approximately 80% [2-4]. These results are not satisfactory, especially for T2 cases. If local recurrence is observed in patients who were initially treated with radiotherapy, the patients will undergo salvage surgery. This results in poorer voice quality. Therefore, it is very important to control the primary tumor lesion. Several studies have reported that chemoradiation was safe and

effective for T2 glottic carcinoma [7-10]. However, there are few published studies that evaluated the effects of chemoradiation for T1b disease.

The purpose of this study was to evaluate the outcomes of patients with T1-T2 glottic carcinoma treated with radiotherapy and to evaluate the effects of chemoradiotherapy for T1b and T2 disease.

Methods

Patient eligibility

At Hiroshima City Asa Citizens Hospital, 49 patients with early glottic carcinoma underwent radiotherapy from July 2006 to December 2015. Eligibility criteria included T1 or T2 disease, age over 20 years, Eastern Cooperative Oncology Group performance status of 0-2, a histologic diagnosis of infiltrative squamous cell carcinoma and no previous radiation therapy (RT) for head and neck neoplasms.

Before therapy, all patients were evaluated clinically with a medical history, physical examination, laboratory examination,

computed tomography (CT) scan of the whole body, and upper endoscopy. The laboratory examination included a complete blood cell count, liver function studies, renal function studies, and measurement of electrolytes. Smoking status was expressed by the Brinkman index, which is calculated as the number of cigarettes per day multiplied by years of smoking.

Treatment procedure for radiotherapy

Three-dimensional (3D) conformal radiation therapy was used for all patients. For 3D treatment planning, CT scanning (Light Speed RT; GE, Milwaukee, Wisconsin) was performed under free-breathing conditions. CT volume data were transferred to a 3D treatment planning system (Xio; ELEKTA, Stockholm, Sweden). Forty-six patients were treated with non-parallel opposed fields using 6-MV photons from the linear accelerator.

In T1 patients, 2 Gy/fraction was used and the total prescribed dose ranged from 60 to 66 Gy (median 60 Gy). In T2 patients, 2 Gy/fraction was used and the total prescribed dose ranged from 60 to 70 Gy (median 60 Gy). Wedge filters of 15 or 30 degrees were used to optimize the dose distribution to achieve a homogeneity of $\pm 5\%$. No prophylactic neck irradiation was performed in any of the cases. All patients were immobilized using a thermoplastic mask during treatment.

Chemotherapy

Eighteen patients (39.1%) were administered chemotherapy. The patients with T1b and T2 carcinoma were administered chemotherapy. The basic regimen was weekly carboplatin (CBDCA, area under the curve [AUC], 1.5-2.0), and 9 patients received this regimen concurrently with RT. Two patients received cisplatin plus 5-fluorouracil concurrently with RT. Seven patients received S-1. Two patients with T1b disease did not undergo chemotherapy because of the presence of various comorbidities.

Evaluation

Tumor response and recurrence were analyzed by the findings of fiberscopes by the otolaryngologist. We also evaluated adverse effects, especially radiation dermatitis and mucositis, using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Follow-up

Patients were followed at regular intervals, usually every month for the first year after treatment, every 2 months for 2 years, every 3 months after 3-4 years and then every 4 months after 5 years if the patient had no evidence of recurrence. The follow-up evaluation routinely included a physical examination, fiberscopes, neck ultrasonography, and blood tests.

Statistical methods

Univariate analyses using the Mantel-Haenszel χ^2 test were performed to determine the statistical significance of differences in responses. The Kaplan-Meier method was used to calculate the local control rates. Statistical significance was defined as $P < 0.05$.

Results

Patient characteristics

Forty-nine patients with T1-T2 carcinoma underwent RT from July 2006 to December 2015. Among them, 46 patients were enrolled and evaluated. Three patients were excluded; one patient was changing hospitals immediately after the treatment and two patients stopped coming to the hospital during or after treatment.

The patients' clinical characteristics are summarized in **Table 1**. The median age was 70.5 years (range, 39-88 years), and 43 patients (93.5%) were men and 3 patients (6.5%) were women. All patients presented with squamous cell carcinoma. Twenty-eight (60.1%) had T1a, 6 (13%) had T1b and 12 (26.1%) had T2 disease. Details of their chemotherapy are shown in **Table 2**.

Local control rate and the pattern of failure

For all 46 patients, the 3 and 5-year local control rates were 88.4% (**Figure 1**). Patients with T1 disease had 3 and 5-year local control rates of 90.9%, while patients with T2 disease had 3 and 5-year local control rates of 80.0% (**Figure 2**). The patients with T1a disease had a 5-year local control rate of 88.9%, while patients with T1b disease had a local control rate of 100% (**Figure 3**). In patients who had T1b disease, none had local recurrence.

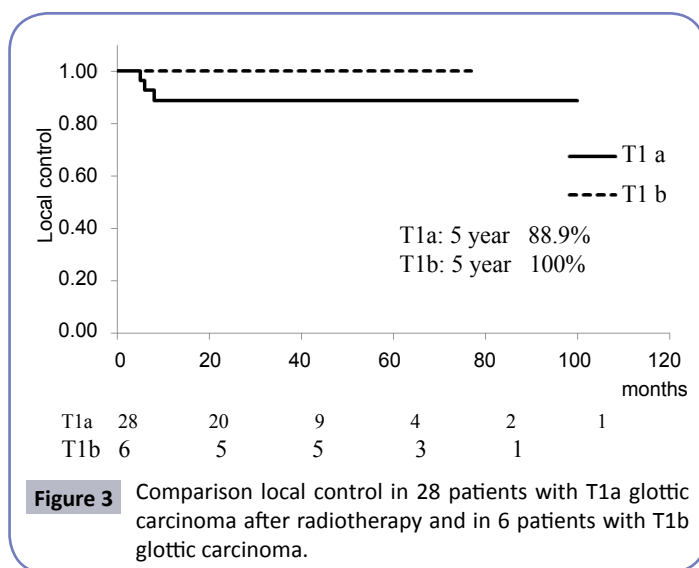
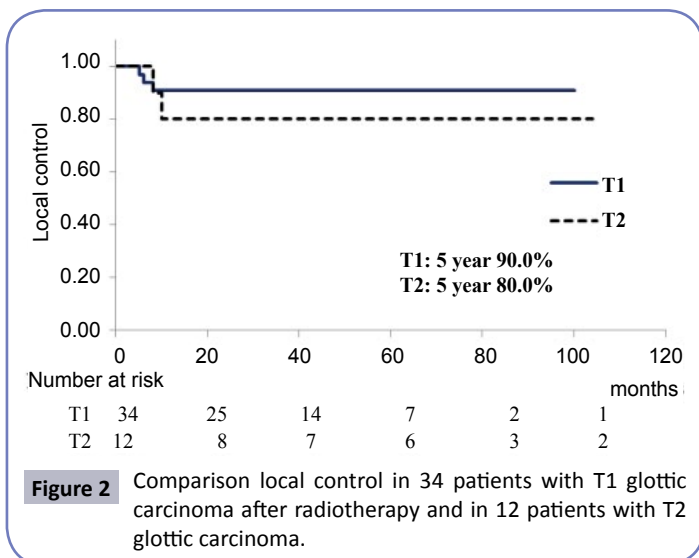
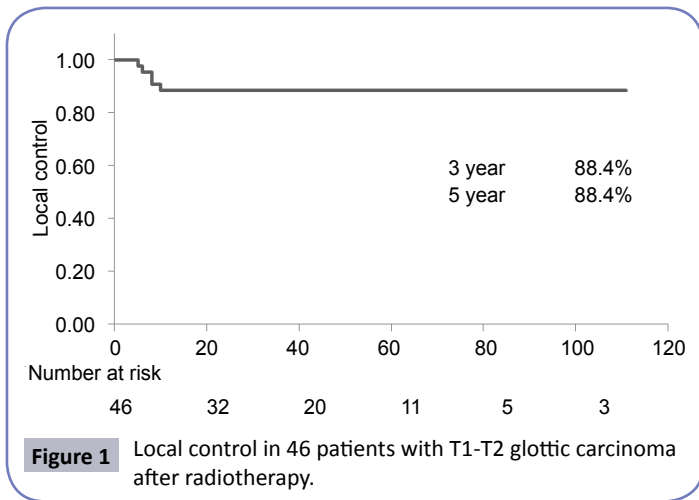
Of the 46 patients, disease recurrence was recorded in 6 patients. Local recurrences occurred in 5 patients (10.9%), and these 5

Table 1 Clinical characteristics of glottic cancer patients.

Gender		percentage
Male	43	93.5
female	3	6.5
Age (median)	39-88 (70.5)	
Performance status (ECOG)		
0-1	46	100
2	0	0
Histology		
Squamous cell carcinoma T factor	46	100
	28	60.9
1b	6	13
2	12	26.1

Table 2 Details of chemotherapy.

T1a patients	
weekly CBDCA	1 patient
TS-1	1 patient
none	26 patients
T1b patients	
weekly CBDCA	3 patients
TS-1	1 patient
none	2 patients
T2 patients	
weekly CBDCA	5 patients
CDDP + 5-FU	2 patients
TS-1	5 patients



patients underwent salvage surgery. One patient had lymph node recurrences in the neck. In the final analysis, only one patient who had T2 disease died of glottic carcinoma.

Overall survival and cause-specific survival

The 3 and 5-year overall survival rates for all patients were 97.4%. The 5-year overall survival rates for T1a, T1b, and T2 were 100%, 100%, and 88.9% respectively. The 3 and 5-year cause-specific survival rates for all patients were 97.4% and 97.4%, respectively. The 5-year cause-specific survival rates for T1a, T1b, and T2 were 100%, 100%, and 88.9% respectively.

Univariate analysis

The variables analyzed in 46 patients included age, T factor, described dose, chemotherapy and Brinkman index for local control (**Table 3**). Age (<75 years) was a significant predictive factor of the local control rate in the univariate analysis (P=0.0463). Although no significant differences were identified, a Brinkman index of ≥ 800 tended to lead to inferior local control (P=0.0579).

Treatment-related toxicities

Grade 1 radiation mucositis was detected in 10 patients (21.7%), grade 2 in 28 patients (60.9%), and grade 3 in 3 patients (6.5%). Grade 1 radiation dermatitis was detected in 32 patients (69.6%), grade 2 in 8 patients (17.4%), and grade 3 in 1 patient (2.8%).

Second primary cancers

Seventeen patients (37.0%) had second primary cancers, and 3 patients (6.5%) had third primary cancers. The sites of second and third primary cancers are shown in **Table 4**. In the 20 primary lesions, 13 lesions (65%) were in the aerodigestive tract.

Table 3 Prognostic factor; univariate analysis.

Prognostic factor		5-year LC (%)	UVA*P
Age, years	<75	96.2	0.0463
	≥ 75	76.5	
T factor	T1	90.9	0.405
	T2	80	
Radiotherapy	60 Gy	85.2	0.376
	>60 Gy	93.8	
Chemotherapy	None	88.9	0.95
	combined	87.5	
Brinkman index**	<800	100	0.0579
	≥ 800	80.8	

*UVA: univariate analyses

**Brinkman index is calculated as the number of cigarettes per day multiplied by years of smoking.

Table 4 Incidence of secondary primary cancers in this study.

Primary site	Number	Percentage
Esophagus	1	5
Stomach	4	20
Lung	4	20
Colon	4	20
Pancreatic	1	5
Bladder	1	5
Prostate	3	15
Others	2	10
Total	20	100

Table 5 Summary of radiation therapy for early glottic carcinoma.

Author (Year)	T factor	No. of patients	Prescribed dose	Local control rate
Nishimura	T1	96	60-66Gy	85%
-1996	T2	32		71%
Burke	T1a	68	65Gy	92%
-1997	T1b	7		80%
	T2a*	18		94%
	T2b*	9		23%
Warde	T1a	403	50Gy	91%
-1998	T1b	46		82%
	T2	286		69%
Onimaru	T1a	146	65Gy	89.80%
-2011	T1b	54		
Harada	T1a	54	66Gy	92%
-2015	T1b	26	70Gy	83%
	T2	35	74.4Gy	86%
This study	T1a	28	60Gy	88.90%
-2016	T1b	6		100%
	T2	12		80%

Discussion

Radiotherapy for early glottic carcinoma shows good clinical outcome. **Table 5** lists the results of radiotherapy studies for early glottic carcinoma. Several studies reported that the 5-year local control rates of T1 disease were approximately 80-90% [11]. In our study, patients with T1 disease had 3 and 5-year local control rates of 90.9%. When compared to other reports, this result is not inferior.

In T1 disease, the T1b glottic carcinoma local control rate, approximately 80%, tends to be lower than it is in T1a disease [2-4]. These results are not satisfactory. However, at present, the standard evidence-based treatment for T1b glottic carcinoma is radiotherapy, not chemoradiotherapy [12]. Several studies reported the results of glottic carcinoma treated with chemoradiotherapy to control the primary tumor lesion; Hirasawa et al. [9] reported that the 5-year local control rate was 83%. In those studies, treatment consisted of radiotherapy in fractions of 2 Gy for a median total dose of 70 Gy, and 30% of the patients with T1b disease were given chemotherapy. In the study reported here, patients with T1b disease were administered chemotherapy concurrently, and had a 5-year local control rate of 100%.

For T2 glottic carcinoma, the 5-year local control rate is 70-80%. Several studies reported that chemoradiation was safe and effective for T2 glottic carcinoma [7-9,13]. Niibe et al. [8] reported that the 5-year local control rate was 83.4%. In that study, treatment consisted of radiotherapy in fractions of 2 Gy for a total dose of 60 Gy, and the patients received chemotherapy concurrently. Akimoto et al. [10] demonstrated that concurrent chemoradiotherapy of T2N0 laryngeal carcinoma produced a better local control rate than conventional radiotherapy alone and reported that the 5-year local control rate was 89%. The chemoradiotherapy method used was a combination of radiotherapy and intravenous chemotherapy. In our study, patients with T2 disease had a 3-year local control rate of 80.0% and a 5-year local control rate of 80.0%, respectively. The results of this study, when compared with previous results, are not inferior.

Various prognostic factors influencing local control were reported. Santhi et al. [11] reported that recurrence of laryngeal cancer was associated with continued smoking which was significant in univariate analysis. Tobacco smoking is the most important etiological factor. Several studies reported that tobacco smoking during radiation therapy for head-and-neck cancer was associated with poor outcomes [14,15]. In our study, no patient who smoked during radiotherapy was observed; therefore, we focused on past history of smoking. Although no significant differences were identified, a Brinkman index ≥ 800 was associated with inferior local control ($P=0.0579$). In addition, age (<75 years) was a significant predictive factor of the local control rate in the univariate analysis ($P=0.0463$).

Conclusion

In our study, patients with T1 disease had a 5-year local control rate of 90.9%, while patients with T2 disease had a local control rate of 80.0%. The patients with T1b disease had a 5-year local control rate of 100%. Chemoradiotherapy for patients with T1b-T2 glottic carcinoma is feasible and may contribute to improved local control in patients with T1b glottic carcinoma.

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Competing and Conflicting Interests

No author has any competing and conflicting interests.

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