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Optimized treatment strategy of radiotherapy for early glottic squamous cell carcinomas: An initial analysis

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ABSTRACT

The purpose of this study was to evaluate the clinical outcomes of radiotherapy for patients with T1/T2 glottic carcinoma. Patients with T1/T2 glottic carcinoma histopathologically diagnosed with squamous cell carcinoma and treated at our hospital between 2007 and 2015 were analyzed retrospectively. Our strategy for T1/T2 glottic carcinoma was as follows: radiotherapy alone with 2.25 Gy per fraction to a total of 25–28 fractions for patients with non-bulky T1 glottic carcinoma; concurrent chemoradiotherapy with oral S-1 and radiotherapy with 2 Gy per fraction to a total of 30 fractions for patients with T1 bulky/T2 favorable glottic carcinoma; or chemoradiotherapy with high-dose cisplatin and radiotherapy with 2 Gy per fraction to a total of 35 fractions for T2 unfavorable glottic carcinoma. Forty-eight patients were eligible. The median follow-up period among surviving patients was 38 months (range, 11–107). The disease was T1a in 23%, T1b in 13%, and T2 in 65% of patients. The 3-year local control rate in all patients, T1a, T1b, and T2 was 96.7%, 100%, 100%, and 96.0%, respectively. Of the 46 patients, one with T2 glottic carcinoma developed recurrent disease at the primary site, and one with T2 glottic carcinoma had lymph node recurrences in the neck. Acute Grade 3 dermatitis occurred in 8 (17%) patients and late Grade 2 hypothyroidism occurred in 2 (4%) patients. This retrospective study shows that our optimized treatment strategy of radiotherapy depending on the stage of early glottic carcinoma is not only effective but also well-tolerated.

Keywords: early glottic cancer, radiotherapy, chemoradiotherapy

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INTRODUCTION

The recommended treatment strategies for early glottic carcinoma (GC) with intent of larynx preservation are mainly definitive radiotherapy (RT) and open organ-preservation surgery.[1,2] However, the outcomes of RT alone for T2 GC are unsatisfactory; the local control (LC) rate has been reported to range from 65%–80%.[3-5] In addition, Reddi *et al.*[6] reported that tumor bulk

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was a highly significant prognostic factor for radiation control, such that patients with bulky T1 tumors had a lower LC rate.

To improve the LC rate for early GC, we designed a concurrent chemoradiotherapy (CCRT) protocol using S-1 for favorable T2 and bulky T1, and we demonstrated the efficacy and safety of this protocol in a prospective study in 2007.[7,8] We also investigated other treatment methods to improve efficacy, because the 5-year LC rates for patients with T1a and T1b lesions in our hospital were insufficient, at 85.9% and 83%, respectively.[9] Therefore, in 2011, for patients with non-bulky T1, we changed the RT dose per fraction from 2.0 Gy to 2.25 Gy, and we reduced the number of fractions from 35 to 28, based on reports that in Japan and overseas, the LC rates for T1 lesions are higher than 90% using 2.25 Gy per fraction.[10,11]

The aim of the present study was to investigate the clinical efficacy of our optimized strategy for T1-T2 glottic carcinoma.

MATERIALS AND METHODS

Figure 1 shows the details of our treatment strategy for early GC at our hospital. We devised this strategy in 2006 for bulky T1 or favorable/unfavorable T2, and in 2011 for non-bulky T1. CCRT with S-1 is not provided now because we enforced this treatment as a clinical trial between January 2006 and March 2016.[7,8]

Patients with biopsy-proven squamous cell carcinoma, no history of RT for head and neck cancer, T1 or T2N0M0, stage I-II GC, and treated with our treatment strategy between June 2007 and December 2015 were included this study. The staging of GC was evaluated by endoscopy, computed tomography (CT) scan, or magnetic resonance imaging (MRI) depending on the TNM system of the American Joint Committee on Cancer (AJCC) seventh edition.[12] The current study was approved by the Institutional Review Board of the Nagoya University Hospital (no.2016-0067).

Because the AJCC staging system[12] does not consider tumor bulk in the substaging of T1 GCs, we classified all T1 GCs as either non-small or bulky, regardless of whether one or both true vocal cords were involved, based on the report by Reddy *et al.*[6] In addition, we classified T2 GCs as either favorable with normal cord mobility or unfavorable with impaired cord mobility based on the ASCO guideline.[2] Finally, the detailed classification was decided after consultation with the cancer board, at which the medical staff members of the departments of radiology, otorhinolaryngology, and clinical oncology and chemotherapy were in attendance.

RT was planned for all patients after appropriate immobilization, with a thermoplastic mask and 3D CT- based techniques. Two parallel-opposed lateral fields were used with a pair of wedge filters. In patients with T2 lesions, the field size was reduced after the administration of about 40 Gy, depending on reduction of the size of the tumor. RT was performed with 4-MV photons at 2.25 Gy/ fraction/ day in the case of RT alone, and at 2.0 Gy/ fraction/ day in the case of CCRT.

Patients with bulky T1 or favorable T2 lesions were treated with CCRT with S-1. The detailed treatment schedule was described previously in our phase I / II study.[7,8] S-1 was taken once daily, 3–6 hours prior to RT, to act as a radiosensitizer. The dose of S-1 was 55.3 mg / m^2/ day, which was determined to be the recommended dose in our phase I study.[8] Patients with unfavorable T2 lesions were treated with CCRT with high-dose CDDP. CDDP was administered intravenously at 80 mg / m^2 tri-weekly concurrently with RT for three courses.[13]

One to 2 months after the end of RT or CCRT, the clinical response was assessed for each patient depending on the combined findings of fiberscopy, CT scanning or MRI. A clinical

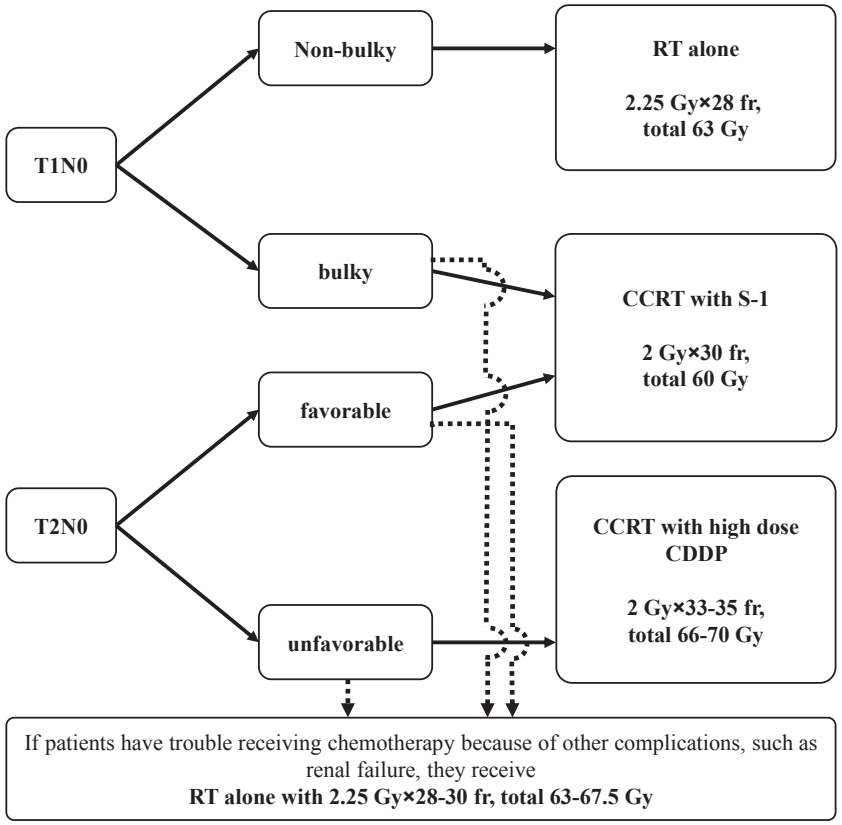

Fig. 1 The treatment strategy in our hospital for T1-2N0M0 glottic squamous cell carcinoma
RT, radiotherapy; Gy, gray; fr, fraction; CCRT, concurrent chemoradiotherapy; CDDP, cisplatin

response (cCR) was defined as a complete disappearance of all measurable lesions by fiberscopy, without any evidence of progression or lymph node metastases by CT or MRI. Patients were monitored for toxicity throughout the treatment. Complete blood counts and blood chemistry measurements were conducted weekly in case of CCRT. Adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. After RT alone or combined with chemotherapy, patients were evaluated at 1-month intervals for the first year, at 2-month intervals during the second year, every 3 months during the third year, every 4 months during the fourth year, and every 6 months thereafter.

OS, LC and disease-specific survival (DSS) rates were calculated using Kaplan-Meier estimates.[14] All statistical analyses were performed with EZR, which is a graphical user interface for R (The R Foundation for Statistical Computing).[15]

RESULTS

Forty-six (95.8%) patients were alive at the time of this analysis (December 27th, 2016), and the median follow-up period was 38.2 months (range, 11.5–107.0) for surviving patients and 35.7 months (range, 11.5–107.0) for all patients. The characteristics of the 48 eligible patients

Table 1 Patient Characteristics

	n	Percent (%)
Total no. of patients	48	100
Age, median (range), y	68.5 (44–94)	
Gender		
Male	46	96
Female	2	4
Performance status (ECOG)		
0	27	56
1	18	38
2	2	4
Unknown	1	2
Smoking status		
Current	21	44
Former	24	50
Never	3	6
T-stage		
T1a	11	23
T1b	6	13
T2	31	65
A-com involvement		
Yes	29	60
No	16	33
Unknown	3	6
Macroscopic classification of tumor		
Superficial	7	15
Exophytic	34	71
Ulcerated/endophytic	4	8
Unclassified	3	6

Abbreviations: ECOG, Eastern Cooperative Oncology Group; A-com, anterior commissure

are shown in Table 1. Twenty-nine (60%) patients had anterior commissure invasion. However, no patient had posterior commissure invasion. Eight (16.7%) of the 48 patients had secondary primary cancers (Table 2). The median duration of RT was 42 days (range, 37–66 days). The selected treatment methods are shown in Table 3. For one patient among the 12 patients with non-bulky T1 GC, RT was interrupted. The patient developed unstable angina and was hospitalized at another hospital after 1 fraction of RT, and RT was restarted after percutaneous coronary angioplasty at another hospital. Therefore, the RT duration was 66 days. Four patients administered CCRT with high-dose CDDP received a high dose of CDDP (tri-weekly, 80 mg/m^2). In one patient, the CDDP dose was reduced to 75% of the initial dose at 2- and 3-courses because of renal failure.

Two of the 48 patients (4.3%) relapsed; 1 patient at the local site, and 1 patient at the regional site. These two patients both had T2 GC with anterior commissure involvement. However, they

Table 2 Incidence of Secondary Primary Cancers

Primary site	n	Percent (%)
Stomach	3	6
Simultaneous	2	4
Synchronous	1	2
Esophagus	1	2
Simultaneous		
Lung	1	2
Synchronous		
Colon	2	4
Simultaneous	1	2
Synchronous	1	2
Bladder	1	2
Synchronous		

Table 3 Selected Treatment Methods

T-stage	n	Radiation	Chemotherapy
T1a			
Non-bulky	10	63 Gy/28 fr	none
Bulky	1	60 Gy/30 fr	S-1 (oral antidrug)
T1b			
Non-bulky	2	63 Gy/28 fr	none
Bulky	3	60 Gy/30 fr	S-1 (oral antidrug)
	1*	63 Gy/28 fr	none
T2			
Favorable	17	60 Gy/30 fr	S-1 (oral antidrug)
	8*	63 Gy/28 fr	none
	2*	67.5 Gy/30 fr	none
Unfavorable	2	66 Gy/33 fr	High-dose cisplatin
	2	70 Gy/35 fr	High-dose cisplatin
Total	48		

*These patients were not able to receive chemotherapy because of advanced age or complications.

received RT alone with 2.25 Gy per fraction because they were elderly. Two of the 48 patients (4.3%) had died by the time of this analysis. One patient, whom we described earlier, died of the disease with favorable T2 GC. Another patient who had T1a GC died of other causes, liver abscess and severe anemia, 17 months after the completion of RT. The patient had untreated diabetes mellitus, simultaneous advanced stomach cancer, and myelodysplastic syndrome. The

local site was controlled until he died. No patient had developed distant metastases by the time of this analysis. The 3-year LC rate for all patients was 97.1% (95% confidence interval [CI];81.4%–99.6%), and the 3-year LC rates for T1a, T1b, and T2 were 100%, 100%, and 96.0% (95% CI: 74.8%–99.4%), respectively. The 3-year OS rate for all patients was 94.1%, and the 3-year OS rates for T1a, T1b, and T2 were 87.5 (95% CI: 38.7%–98.1%), 100%, and 95.5% (95% CI: 71.9%–99.3%), respectively. The 3-year DSS rate for all patients was 96.4% (95% confidence interval [CI];77.2%–99.5%), and the 3-year DSS rates for T1a, T1b, and T2 were 100%, 100%, and 95.7% (95% CI: 71.9%–99.3%), respectively. When we excluded patients who received RT alone because of age or complications, the LC, OS, and DSS rates of T2 patients each became 100%.

Acute Grade 3 mucosal and skin toxicities were detected in 1 (2.0%) and 8 (16.7%), respectively. Regarding acute hematological toxicities and late toxicity, no severe (up to Grade 3) complications have been observed to date. Of two patients who developed late Grade 2 hypothyroidism, one patient underwent partial thyroidectomy concurrent with total laryngectomy for local recurrence.

DISCUSSION

Even if GC is T1 or T2, it is thought to have a wide variety of pathophysiologies based on the size (bulky or non-bulky) or characterization (superficial, exophytic, ulcerated) of the tumor. Recently, Bhateja *et al.*[16] subdivided patients with T2 disease into T2a and T2b based on cord mobility, with patients with T2b disease demonstrating a partially hypomobile cord. Treatment of T2bN0 versus T2aN0 disease with RT alone was significantly associated with inferior LC. There are several reports on the use of CRT in patients with T2 GC. A multi-institutional[17] Japanese study and a single-center[18] Japanese study reported an improvement in the 5-year LC, OS and disease-free survival for T2 GC with the addition of chemotherapy. Considering these studies, it is thought that T2 GC should be treated with RT along with a chemotherapy regimen, and it might be necessary to change the strength of the regimen depending on the presence of impaired cord mobility. However, these studies do not subclassify patients more precisely. Therefore, we suggest that a more appropriate strategy of subdividing every stage of GC with a classification more detailed than TNM is needed, and we have based our treatment on an optimized strategy for early GC that classifies T1 lesions into bulky or non-bulky, and T2 lesions into favorable or unfavorable. First, we developed the CCRT protocol with S-1 in 2006, and showed its efficacy.[7,8] In this study, 21 patients were treated with CCRT with S-1, and all of them were alive without disease at the time of this analysis. Second, we changed the RT dose for non-bulky T1 GC from 2.0 Gy to 2.25 Gy per fraction in 2011. In addition to that, Itoh *et al.*[19] showed results of the 2.25 Gy method and comparable efficacy and acceptable safety compared to a 2.0 Gy method in a multicenter survey of the TOSTRO in Japan.

Because there is a small number of locoregional failure and overall death events, it is difficult to examine a statistical prognostic factor. Several prognostic factors for GC have been reported,[3] and anterior commissure involvement is known as a poor prognostic factor.[3,6] In our study, a patient who developed local failure had T2 disease with anterior commissure involvement, comparable to the results of existing reports. Furthermore, some biomarkers have been reported as prognostic factors for LC.[20-23] For example, the overexpression of cycloxygemase-2 (COX-2), p53,[20] epithelial cell adhesion molecule (EpCAM),[21] hypoxia inducible factor 1α subunit (HIF1α), and carbonic anhydrase IX (CA-IX)[22] have been reported as risk factors for high local recurrence rate, and high total microvessel perimeter per tumor area (TP/TA) is a predictor for

radiosensitivity in early-stage GC.[23] Changes in these biomarkers could reflect the difference in the LC rate for T1-2 GC by RT alone. Therefore, even if some patients have molecular expression of a poor-prognosis gene, the treatment outcome might be improved by a mechanism such as radiosensitive reinforcement of chemotherapy, exceeding the limit of the RT alone. In the future, by performing fundamental experiments and identifying prognostic factors, patients with radiation resistance and more desirable for CCRT may be chosen.

Both patients with recurrence in our study had favorable T2 GC and were suitable to receive chemotherapy when considering out treatment strategy. However, because they were elderly, they received RT alone. Meanwhile, all the patients who were treated with our strategy are alive without recurrence. Therefore, establishing the proper treatment strategy for patients who cannot receive chemotherapy is the forthcoming challenge. When chemoradiotherapy is not appropriate because of old age or complications such as renal dysfunction, RT alone is usually selected. Therefore, as a solution to this problem, we planned a new protocol of CCRT with S-1 (UMIN000023416) and started a new clinical trial (currently at the stage of patient registration). In our new protocol, we improved the old protocol by reducing the S-1 administration period to 5 weeks while maintaining the daily dose, reducing the RT dose to 2.25 Gy per fraction for a total of 25 fractions, and expanding the eligiblity criteria to include patients 75 to 80 years of age. With these improvements, we will be able to examine the efficacy and safety of chemotherapy in older patients.

In conclusion, although the sample size was small, and the follow-up duration was short in the present study, it suggests that we should reconsider the strategy of the RT for early GC. We will continue to investigate the optimized strategy for non-bulky T1 and unfavorable T2 GC, to assess each patient, and to examine the effectiveness and the safety of this method in our new clinical trial for bulky T1 and favorable T2 GC.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1) National Cancer Institute at the National Institutes of Health (2016), NCCN Guidelines Version 2.2016 Cancer of the Glottic Larynx. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf
2) Pfister DG, Laurie SA, Weinstein GS, Mendenhall WM, Adelstein DJ, Ang KK *et al.* American Society of Clinical Oncology clinical practice guideline for the use of larynx-preservation strategies in the treatment of laryngeal cancer. *J Clin Oncol*, 2006; 24: 3693–3704.
3) Mendenhall WM, Werning JW, Hinerman RW, Amdur RJ and Villaret DB: Management of T1-T2 glottic carcinomas. *Cancer*, 2004; 100: 1786–1792.
4) Mendenhall WM, Mancuso AA, Amdur RJ and Werning JW: Laryngeal Cancer. In: Perez and Brady's Principles and Practice of Radiation Oncology. 6th edition. Halperin EC, Perez CA and Brady LW (Eds.). Philadelphia: Lippincott William & Wilkins, pp. 850–868, 2013.
5) Frata P, Cellai E, Magrini SM, Bonetti B, Vitali E, Tonoli S, Buglione M, Paiar F, Barca R, Fondelli S, Polli C, Livi L and Biti G: Radical radiotherapy for early glottic cancer: Results in a series of 1087 patients from two Italian radiation oncology centers. II. The case of T2N0 disease. *Int J Radiat Oncol Biol Phys*, 2005; 63: 1387–1394.
6) Reddy SP, Hong RL, Nagda S, Emami B. Effect of tumor bulk on local control and survival of patients with T1 glottic cancer: a 30-year experience. *Int J Radiat Oncol Biol Phys*, 2007; 69: 1389–1394.
7) Kimura K, Itoh Y, Okada T, Nakahara R, Kawamura M, Kubota S, *et al.* Critical evaluation of a prospective study of concurrent chemoradiotherapy with s-1 for early glottic carcinoma. *Anticancer Res*, 2015; 35: 2385–2390.

8) Fujimoto Y, Kato S, Itoh Y, Naganawa S, Nakashima T. A phase I study of concurrent chemoradiotherapy using oral s-1 for head and neck cancer. *Anticancer Res*, 2014; 34: 209–213.
9) Hirasawa N, Itoh Y, Ishihara S, Kubota S, Itoh J, Fujimoto Y, *et al.* Radiotherapy with or without chemotherapy for patients with T1-T2 glottic carcinoma: retrospective analysis. *Head & neck oncology*, 2010; 2: 20.
10) Mendenhall WM, Amdur RJ, Morris CG, Hinerman RW. T1-T2N0 squamous cell carcinoma of the glottic larynx treated with radiation therapy. *J Clin Oncol*, 2001; 19(20): 4029–4036.
11) Yamazaki H, Nishiyama K, Tanaka E, Koizumi M, Chatani M. Radiotherapy for early glottic carcinoma (T1N0M0): results of prospective randomized study of radiation fraction size and overall treatment time. *Int J Radiat Oncol Biol Phys*, 2006; 64: 77–82.
12) Sobin L, Gospodarowicz M, Wittekind C, eds. TNM Classification of malignant tumors. 7th ed. Hoboken, NJ: John Wiley & Sons, Inc., 2009.
13) Kiyota N, Tahara M, Okano S, Kawashima M, Matsuura K, Onozawa Y, *et al.* Phase II feasibility trial of adjuvant chemoradiotherapy with 3-weekly cisplatin for Japanese patients with post-operative high-risk squamous cell carcinoma of the head and neck. *Jpn J Clin Oncol*, 2012; 42: 927–933.
14) Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*, 1958; 53: 457–481.
15) Kanda Y. Investigation of the freely available easy-to use software 'EZR' for medical statistics. *Bone Marrow Transplant*, 2013; 48: 452–458.
16) Bhateja P, Ward MC, Hunter GH, Greskovich JF, Reddy CA, Nwizu TI, *et al.* Impaired vocal cord mobility in T2N0 glottic carcinoma: Suboptimal local control with Radiation alone. *Head Neck*, 2016; 38: 1832–1836.
17) Hirasawa N, Itoh Y, Naganawa S, Ishihara S, Suzuki K, Koyama K, *et al.* Multi-institutional analysis of early glottic cancer from 2000 to 2005. *Radiat Oncol*, 2012; 7: 122.
18) Akimoto T, Nonaka T, Kitamoto Y, Ishikawa H, Ninomiya H, Chikamatsu K, *et al.* Radiation therapy for T2N0 laryngeal cancer: A retrospective analysis for the impact of concurrent chemotherapy on local control. *Int J Radiat Oncol Biol Phys*, 2006; 64: 995–1001.
19) Itoh Y, Kubota S, Kawamura M, Nomoto Y, Maruo Takayuki, Yamakawa K, *et al.* A multicenter survey of stage T1 glottic cancer treated with radiotherapy delivered in 2.25-Gy fractions in clinical practice: An initial 5-year analysis. *Nagoya J. Med. Sci*, 2016, 78: 399–406.
20) Cho EI, Kowalski DP, Sasaki CT, Haffty BG. Tissue microarray analysis reveals prognostic significance of COX-2 expression for local relapse in T1-2N0 larynx cancer treated with primary radiation therapy. *Laryngoscope*, 2004; 114: 2001–2008.
21) Murakami N, Mori T, Yoshimoto S, Ito Y, Kobayashi K, Ken H, *et al.* Expression of EpCAM and prognosis in early-stage glottic cancer treated by radiotherapy. *Laryngoscope*, 2014; 124: E431–436.
22) Schrijvers ML, van der Laan BF, de Bock GH, Pattje WJ, Mastik MF, Menkema L, *et al.* Overexpression of intrinsic hypoxia markers HIF1alpha and CA-IX predict for local recurrence in stage T1-T2 glottic laryngeal carcinoma treated with radiotherapy. *Int J Radiat Oncol Biol Phys*, 2008; 72: 161–169.
23) Zhang S, Hayashi R, Fujii M, Hasegawa Y, Yoshino K, Fukayama M, *et al.* Total microvessel perimeter per tumor area is a predictor of radiosensitivity in early-stage glottic carcinoma. *Int J Radiat Oncol Biol Phys*, 2009; 73: 1104–1109.