ORIGINAL PAPER

Nagoya J. Med. Sci. **85**. 241–254, 2023
doi:10.18999/nagjms.85.2.241

Optimized radiotherapy treatment strategy for early glottic carcinoma

Tamami Ono[1], Yoshiyuki Itoh[2], Shunichi Ishihara[1], Mariko Kawamura[1], Yumi Oie[1], Yuuki Takase[1], Masayuki Okumura[1], Hidekazu Oyoshi[3], Naoya Nagai[1] and Shinji Naganawa[1]

[1]*Department of Radiology, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[2]*Department of Radiology, Anjyo Kosei Hospital, Anjyo, Japan*
[3]*Department of Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

ABSTRACT

The local control rates of T1 bulky and T2 glottic carcinoma treated via radiation therapy alone are unsatisfactory; thus, we aimed to evaluate the efficacy and safety of our treatment protocol for early glottic carcinoma. Patients with early glottic squamous cell carcinoma treated via radiation therapy from January 2007 to November 2019 were reviewed. Patients were treated with: 63–67.5 Gy/28–30 fractions of radiation therapy alone for T1 non-bulky; concurrent chemoradiotherapy with S-1 and 60 Gy/30 fractions for T1 bulky and T2 favorable; and concurrent chemoradiotherapy with high-dose cisplatin and 66–70 Gy/33–35 fractions for T2 unfavorable glottic carcinoma. Local failure rates were estimated using the cumulative incidence function, overall and disease specific survival rates were estimated using Kaplan-Meier analysis, and adverse events were evaluated. Eighty patients were analyzed; the median age was 69.5 (range, 26–90) years, the median follow-up time for survivors was 40.1 (range, 1.9–128.4) months, and the 3-year local failure, disease specific survival, and overall survival rates were 5.8%, 98.3%, and 94.4%, respectively. In T1 bulky and T2 cases, the local failure rate was significantly lower in the concurrent chemoradiotherapy than in the radiation therapy alone group. Grade 3 acute dermatitis and mucositis were noted in nine and four patients, respectively. There were no acute adverse events of Grade 4 or higher, or late adverse events of Grade 2 or higher. The treatment protocol was effective and well-tolerated; thus, the efficacy of concurrent chemoradiotherapy was suggested in T1 bulky and T2 cases.

Keywords: early glottic carcinoma, radiation therapy, chemoradiotherapy

Abbreviations:
GC: glottic carcinoma
RT: radiation therapy
LC: local control
CCRT: concurrent chemoradiotherapy
CDDP: cisplatin
LF: local failure
OS: overall survival
DSS: disease specific survival
AEs: adverse events

Received: March 30, 2022; accepted: May 27, 2022
Corresponding Author: Tamami Ono, MD
Department of Radiology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
Tel: +81-52-744-2328, Fax: +81-52-744-2335, E-mail: tamami.ono@med.nagoya-u.ac.jp

INTRODUCTION

The goals of treatment for early glottic carcinoma (GC) are tumor eradication and preservation of larynx functions, including speaking and swallowing. The recommended treatment strategy for early GC is partial laryngectomy, including endoscopic and open resection, and definitive radiation therapy (RT); generally, the efficacies of resection and RT are comparable.[1,2] Previous studies have shown that the local control (LC) rate of early stage GC varies widely, while that of RT alone for T2 GC is unsatisfactory, ranging from 65% to 80%.[3-5] Reddy et al[6] reported that tumor size is an important prognostic factor for the LC rate in T1 GC, and that the LC rate is lower in T1 bulky tumors. Several studies have subclassified T2 GC into T2a and T2b, reporting lower LC rates in T2b.[7-9] In this study, we subclassified T1 and T2 GCs into T1 nonbulky, T1 bulky, T2 favorable, and T2 unfavorable, following previous reports.

We first designed a concurrent chemoradiotherapy (CCRT) protocol using S-1 (tegafur, gimeracil, and oteracil) for T1 bulky and T2 favorable GCs with the aim of improving the LC rate; the efficacy and safety of this protocol was demonstrated in our previous phase I/II study.[10,11] S-1 is an orally administered antineoplastic agent shown to be effective against a variety of solid tumors including head and neck cancer. Due to the inadequate results observed in our previous experiments regarding CCRT with low-dose cisplatin (CDDP)/5-fluorouracil for T2 GC,[12,13] we were concerned that CCRT with S-1 may be inadequate in patients with T2 unfavorable GC; thus, CCRT with high-dose CDDP was selected. Furthermore, we changed the RT dose from 2.0 Gy/fraction to 2.25 Gy/fraction, thereby reducing the number of fractions from 35 to 28 for patients with T1 nonbulky GC. This was based on reports, from Japan as well as overseas, that the LC rates for T1 tumors were higher than 90% when using 2.25 Gy/fraction.[14,15] Our research group also reported comparable efficacy and acceptable safety of the 2.25 Gy/fraction method, compared with the conventional 2.0 Gy/fraction method, in a multicenter survey of the Tokai Study Group for Therapeutic Radiology and Oncology conducted in Japan from 2011 to 2015.[16] A recent meta-analysis by Benson et al,[17] including several randomized controlled trials, also reported that hypofractionation for early GC is effective for improving LC rates.

The overall results of our optimized treatment strategy were reported in 2017, demonstrating that our protocol, which has been used in our institution since 2007,[18] was both effective and well tolerated.[19] The purpose of this study was to evaluate the clinical efficacy of our optimized treatment strategy in early GC in a larger cohort.

MATERIALS AND METHODS

Patients

This study was approved by the Institutional Review Board of Nagoya University Hospital (reference number: 2020-0018) and conducted in accordance with the 1964 Declaration of Helsinki and subsequent amendments. Informed consent was obtained from all study participants prior to initial treatment.

Patients with T1 or T2N0M0 (stage I–II) glottic squamous cell carcinoma—treated via definitive RT at Nagoya University Hospital between January 2007 and November 2019—were included in the study. The histological diagnoses were confirmed by biopsy, and all tumors were staged according to the eighth edition of the Union for International Cancer Control staging classification

system.[20] In addition, T1 and T2 GC were substaged. T1 bulky tumors were defined as tumors extending over the entire true vocal fold, and/or horseshoe-shaped tumors extending over the anterior commissure and one-third of both true vocal folds; T1 nonbulky tumors were defined as tumors that did not extend over these boundaries, based on the report by Reddy et al[6] T2 favorable tumors were defined as tumors with normal vocal fold mobility; T2 unfavorable tumors were defined as tumors with impaired vocal fold mobility, based on previous studies.[7-9] The treatment policy for each patient was established in a conference attended by both otolaryngologists and radiation oncologists, and the final treatment modality was selected based on the patient's wishes.

Treatment

Figure 1 shows the details of the treatment protocol for early GC at our institution; RT was performed for all patients once a day on weekdays, ie, five times a week, with no irradiation on holidays. Patients with T1 nonbulky lesions were treated with 28–30 fractions of RT alone at 2.25 Gy/fraction per day. Patients with T1 bulky or T2 favorable GC were treated with CCRT using S-1. S-1 was taken once daily, 3–6 h prior to RT; RT was initiated on the same day as S-1 administration, and the patients were treated with 30 fractions at 2.0 Gy/fraction per day. S-1 was not administered on days when RT was not performed; the dose of S-1 was 55.3 mg/m^2 per day, the recommended dose determined in our phase I/II study.[10,11] Patients with T2 unfavorable lesions were treated with CCRT using high-dose CDDP. CDDP was administered intravenously at 80mg/m^2 tri-weekly concurrently with RT for three courses. Patients were treated with 33–35 fractions of RT at 2.0 Gy/fraction per day, initiated on the same day as CDDP administration. Patients who were not eligible for CCRT due to advanced age or renal dysfunction were treated with 28–30 fractions of RT alone at 2.25 Gy/fraction per day.

All patients were immobilized in the supine position wearing a thermoplastic mask and underwent computed tomography (CT) simulation without contrast enhancement. RT was delivered

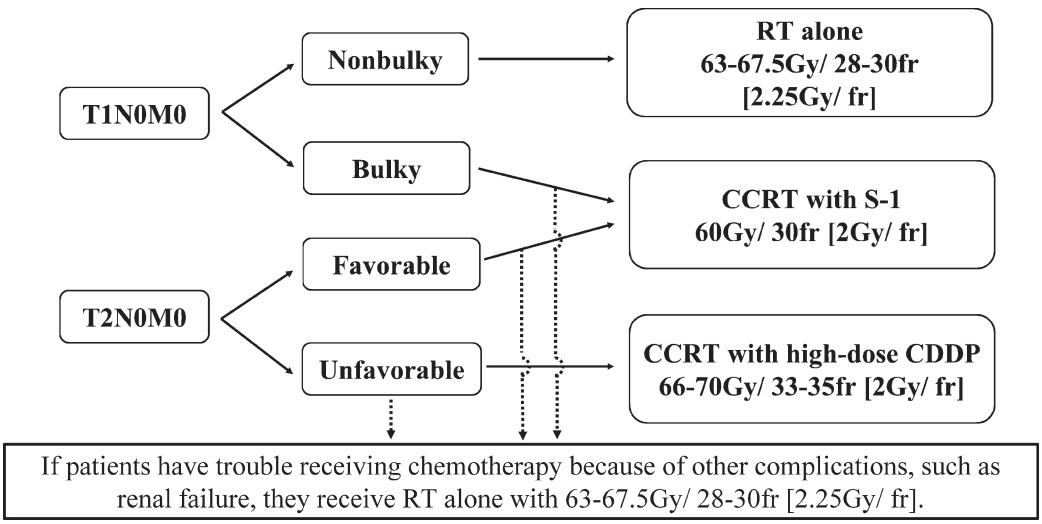


Fig. 1 Our optimized treatment strategy

RT: radiation therapy
fr: fraction
CCRT: concurrent chemoradiotherapy
CDDP: cisplatin

using a 4 MV photon beam with 3D-CT-based technology. Two parallel-opposed lateral fields were used to set up a rectangular irradiation field of 6 × 6 cm in most cases, and a pair of 15° or 30° wedge filters were used to optimize the dose distribution. In patients with T2 GC, we first used a slightly larger field size for irradiation upto 40 Gy than in T1 GC patients; thereafter, the field size was reduced depending on the reduction in tumor size.

Outcome measures

The outcomes of this study were the evaluations of efficacy and safety of our optimized treatment protocol in early GC; this included the assessment of clinical response, local failure (LF) rate, overall survival (OS) rate, disease specific survival (DSS) rate, and adverse events (AEs) in all patients. One to two months after completing RT or CCRT, the clinical response of each patient was evaluated by combining the fiberscopic, CT, and magnetic resonance imaging findings. A clinical response was defined as the complete disappearance of all measurable lesions (determined by the otolaryngologist via fiberscopy), as well as no evidence of progression or lymph node metastases (determined by the radiologist via CT or magnetic resonance imaging). LF was defined as including both local recurrence alone and local recurrence with regional lymph node recurrence. Patients were monitored for AEs at 1-week intervals during treatment, 1-month intervals during the first year, 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. AEs were classified according to the Common Terminology Criteria for Adverse Events Version 4.0.

Statistical analysis

OS, DSS and LC rates were analyzed using the Kaplan-Meier method with the log-rank test. The LF curves were estimated using the cumulative incidence function—considering the competing risk of death without LF—and compared using Gray's test. All statistical analyses were performed using EZR (The R Foundation for Statistical Computing, Vienna, Austria), a graphical user interface for R.[21]

RESULTS

A total of 80 patients were analyzed. The median follow-up time for survivors was 40.1 (range, 1.9–128.4) months, the median duration of RT treatment was 42 (range, 37–66) days, and the median number of days off irradiation was 2 (range, 0–21) days. There were two patients who discontinued irradiation during the treatment period: one patient had a 21-day irradiation pause due to the onset of unstable angina during RT, the other had a 9-day irradiation pause due to fever caused by side effects of chemotherapy. Patient characteristics are shown in Table 1; the median age was 69.5 (range, 26–90) years, 77 (96%) patients were male, and 14 (18%) had another primary cancer prior to or concurrent with RT. Anterior and posterior commissure invasion occurred in 38 (48%) and 10 (13%) patients, respectively.

Details of the treatment are shown in Table 2; 51 (64%) patients were treated via RT alone through 28–30 fractions of 2.25 Gy/fraction per day. Exceptionally, one patient was treated with 35 fractions of RT alone at 2.0 Gy/fraction per day, as a subglottic skip lesion was suspected via fiberscopy; although deemed pathologically negative, the irradiation area was prophylactically expanded. Twenty-nine patients were treated with chemotherapy, receiving 30–35 fractions of RT at 2.0 Gy/fraction per day; 22 (76%) patients received S-1, six (21%) received CDDP, and one (3%) received UFT which components are tegafur and uracil. Patients treated with UFT received sequential chemotherapy before and after RT at other hospitals. One patient who received S-1 was

Table 1 Characteristics of the patients

		n	Percent (%)
Total no. of patients		80	100
Age, median (range), y	69.5 (26-90)		
Gender			
Male		77	96
Female		3	4
Performance status (ECOG)			
0		41	51
1		37	46
2		2	3
T stage			
T1a		27	34
Nonbulky		22	28
Bulky		5	6
T1b		13	16
Nonbulky		9	11
Bulky		4	5
T2		40	50
Favorable		33	41
Unfavorable		7	9
A-com involvement			
Yes		38	48
No		42	52
P-com involvement			
Yes		10	13
No		70	87
Macroscopic classification of tumor			
Superficial		36	45
Exophytic		41	51
Unclassified		3	4
Another primary cancer prior to or concurrent with RT			
Yes		14	18
No		66	82
Smoking			
Yes		73	91
No		7	9
Alcohol			
Yes		66	83
No		14	17

ECOG: Eastern Cooperative Oncology Group
A-com: anterior commissure
P-com: posterior commissure

Table 2 Treatment details

Radiation [1 dose/ fr]	Total dose/ fr	Number of patients (%) (n = 80)
[2.25Gy/ fr]	67.5Gy/ 30fr (RT alone)	14 (18)
	63Gy/ 28fr (RT alone)	36 (45)
	56.25Gy/ 25fr (CCRT with S-1)	1 (1)
[2Gy/ fr]	60Gy/ 30fr (CCRT with S-1)	21 (26)
	66Gy/ 33fr (CCRT with CDDP)	3 (4)
	70Gy/ 35fr (CCRT with CDDP or RT alone)	5 (6)
Chemotherapy	Types of chemotherapy	Number of patients (%) (n = 29)
	S-1	22 (76)
	CDDP	6 (21)
	UFT	1 (3)

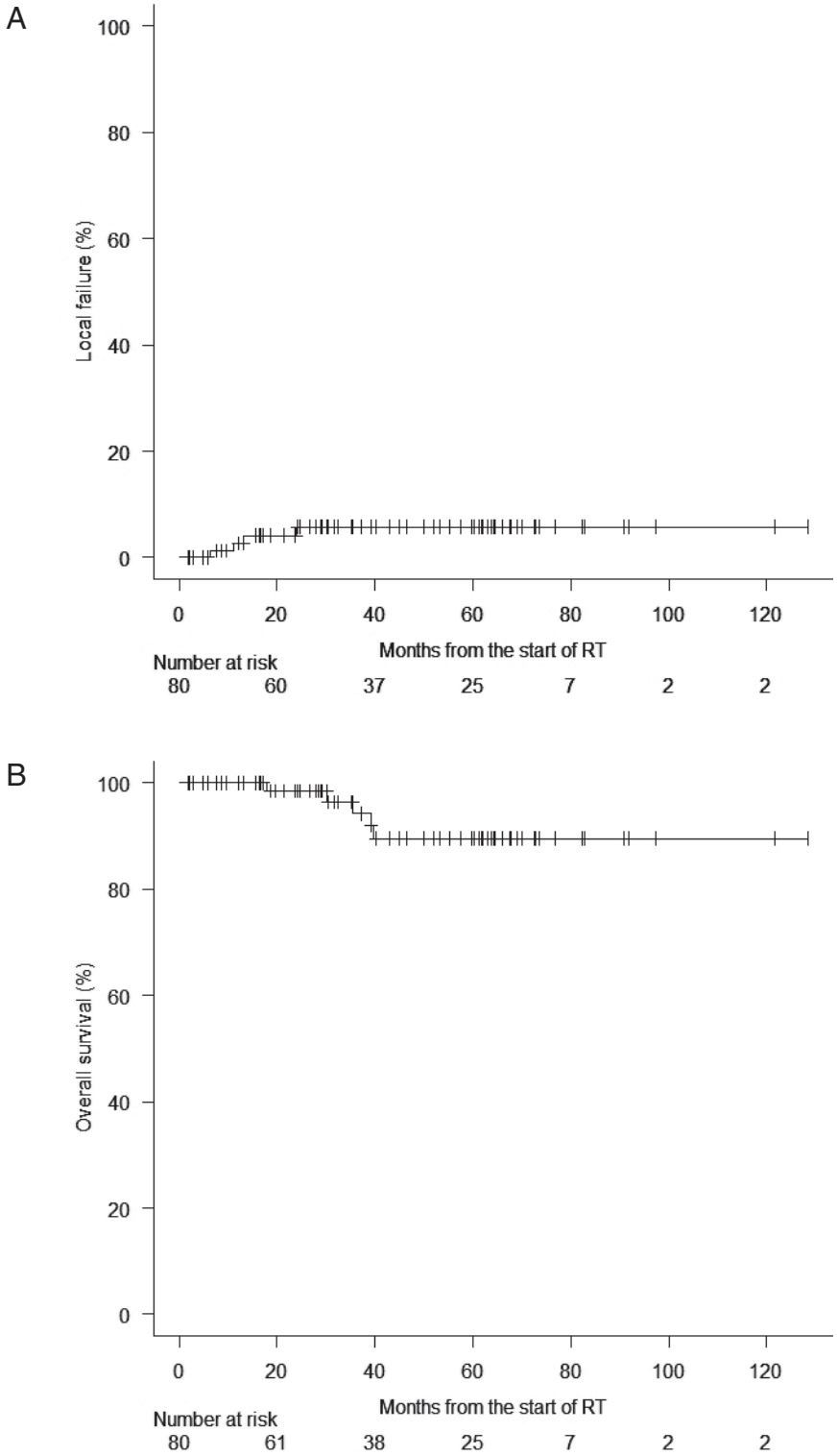
fr: fraction
RT: radiation therapy
CCRT: concurrent chemoradiotherapy
CDDP: cisplatin
UFT: tegafur and uracil

treated with 25 fractions of 2.25 Gy/fraction per day; this was performed according to our new CCRT protocol[22] aimed at shortening the treatment time. The remaining patients who received S-1 or CDDP were treated according to the study protocol. The initial response to treatment was complete response in all cases, except for one patient who was transferred to the hospital before assessment.

Overall outcomes are shown in Figure 2. Among all patients, the 3-year LF rate was 5.8% (95% CI, 1.8–13.1); the 3-year OS and DSS rates were 94.4% (95% CI, 83.4–98.2) and 98.0% (95% CI, 86.6–99.7), respectively. In the univariate analysis, the LF, OS and DSS rates did not show any statistically significant association with either clinical or tumor characteristics. Recurrence and death occurred in five patients each. All five recurrent patients were treated with RT alone: one was a T1 nonbulky case and four were T2 cases; of these, three patients developed only local recurrence, one developed only regional lymph node recurrence, and one developed both local recurrence and regional lymph node recurrence. All patients underwent either salvage surgery, salvage radiotherapy, or both. Four recurrent patients achieved progression-free survival, and one patient died of aspiration pneumonia after salvage surgery; the remaining four of five patients died from secondary primary cancers.

The cumulative incidence curves of LF by tumor classification are shown in Figure 3. The 3-year LF rates in the T1 and T2 groups were 2.9% (95% CI, 0.2–13.2) and 8.1% (95% CI, 2.0–19.8), respectively (p=0.39). The 3-year LF rates in the T1 nonbulky, T1 bulky, T2 favorable, and T2 unfavorable groups were 3.7% (95% CI, 0.3–16.2), 0% (95% CI, 0–0), 6.8% (95% CI, 1.2–19.8), and 14.3% (95% CI, 0.5–49.1), respectively.

We subcategorized T1 bulky and T2 patients into the CCRT and RT alone groups to evaluate the efficacy of CCRT; four patients who discontinued chemotherapy due to AEs, and one patient who received sequential UFT chemotherapy, were excluded. Finally, there were 24 patients in the CCRT group and 20 patients in the RT alone group. The cumulative incidence curves for LF in


A
Local failure (%)
100
80
60
40
20
0
0
20
40
60
80
100
120
Months from the start of RT
Number at risk
80
60
37
25
7
2
2
B
Overall survival (%)
100
80
60
40
20
0
0
20
40
60
80
100
120
Months from the start of RT
Number at risk
80
61
38
25
7
2
2

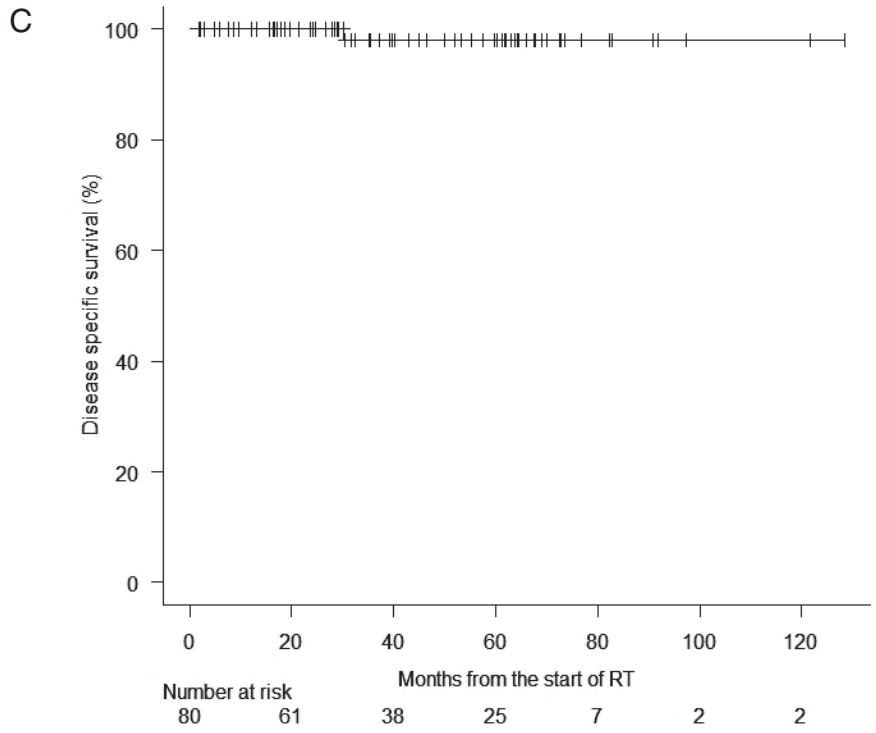
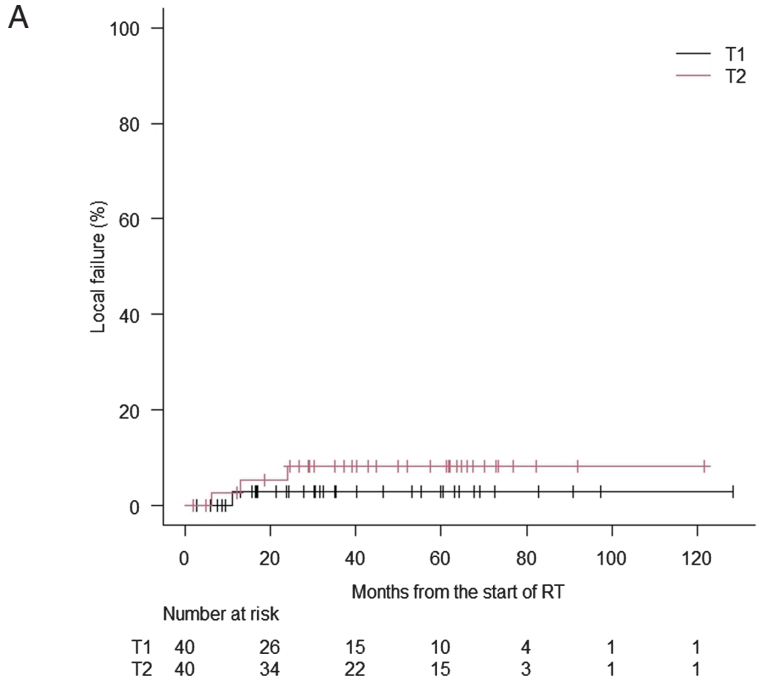


Fig. 2 Overall outcomes
Fig. 2A: Cumulative incidence curves of local failure among all patients.
Fig. 2B: Kaplan–Meier curves of overall survival among all patients.
Fig. 2C: Kaplan–Meier curves of disease specific survival among all patients.
RT: radiation therapy

the two groups are shown in Figure 4. The 3-year LF rate was significantly lower in the CCRT than the RT alone group (0% [95% CI, 0–0] vs 19.9% [95% CI, 4.4–43.3]; p=0.025). The patients treated via RT alone who could not receive CCRT had a single or multiple reasons for deviating from our protocol, including advanced age; underlying diseases, such as renal dysfunction or heart failure; treatment strategy considering secondary primary cancers; and patient convenience. Two patients discontinued chemotherapy due to renal failure, one due to laryngeal bleeding, and one due to fever as a side effect. The patient with fever discontinued S-1 on day 29; only RT was restarted on day 34, administered to 70 Gy. The other three patients who discontinued chemotherapy continued RT as per our protocol.

Table 3 shows the AEs. Grade 3 acute AEs were noted in 10 patients overall: three patients (30%) treated with CCRT, and seven (70%) treated with RT alone. Grade 3 dermatitis was noted in nine patients (11%), and mucositis in four patients (5%). There were no acute AEs of grade 4 or higher, or late AEs of grade 2 or higher.



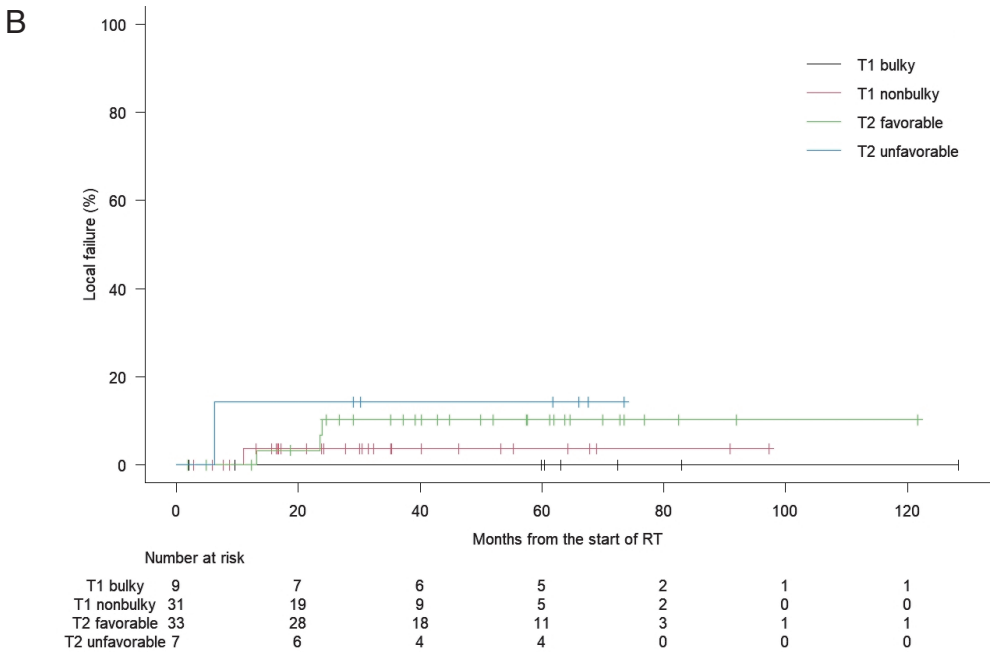


Fig. 3 Cumulative incidence curves

Fig. 3A: Cumulative incidence curves of local failure in the T1 (black) and T2 (red) groups.

Fig. 3B: Cumulative incidence curves of local failure in the T1 bulky (black), T1 nonbulky (red), T2 favorable (green), T2 unfavorable (blue) groups.

RT: radiation therapy

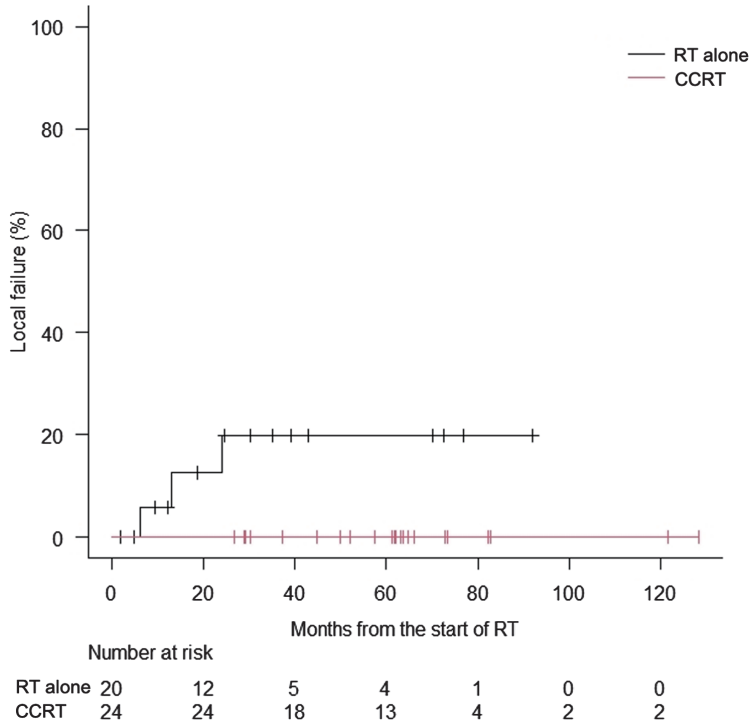


Fig. 4 T1 bulky/T2 cases
Cumulative incidence curves of local failure in the RT alone (black) and CCRT (red) groups.
RT: radiation therapy
CCRT: concurrent chemoradiotherapy

Table 3 AEs (CTCAE v4.0)

	Grade (n = 80) Number of patients (%)			
	no AEs	grade 1	grade 2	grade 3
Acute				
Dermatitis	1 (1)	31 (39)	39 (49)	9 (11)
Mucositis	5 (6)	49 (61)	22 (28)	4 (5)
Laryngeal edema	32 (40)	48 (60)	0 (0)	0 (0)
Laryngeal hemorrhage	74 (93)	6 (7)	0 (0)	0 (0)
Laryngeal pain	7 (9)	68 (85)	5 (6)	0 (0)
Late				
Hoarseness	50 (63)	30 (37)	0 (0)	0 (0)
Soft tissue necrosis	80 (100)	0 (0)	0 (0)	0 (0)
Laryngeal edema	79 (99)	1 (1)	0 (0)	0 (0)
Laryngeal hemorrhage	80 (100)	0 (0)	0 (0)	0 (0)
Laryngeal pain	75 (94)	5 (6)	0 (0)	0 (0)

AEs: adverse events
CTCAE v4.0: Common Terminology Criteria for Adverse Events version 4.0

DISCUSSION

We have been treating early GC with our optimized treatment strategy—shown in Figure 1—since 2007; its safety and efficacy were reported in our initial report in 2017.[19] In this study, we increased the number of patients and reevaluated the safety and efficacy of this treatment strategy. Mostly, the 3-year OS and DSS rates of all patients were similar or slightly better than observed in our previous report. The 3-year LC of all patients was also good; however, the occurrence of relapses slightly increased compared with our previous report. Four of the five relapses were T2 cases where the treatment strategy was changed from CCRT to RT alone; thus, the strategy deviated from our treatment protocol. The LF rates in this study were generally comparable to those reported in several randomized controlled trials regarding patients treated via altered-fractionation radiotherapy,[15,17,23,24] whether in the T1-2, T1, or T2 group. AEs were generally comparable to our previous report and other randomized controlled trials.[17,19,23,24]

In this study, we performed sub-analyses to evaluate the efficacy of CCRT in T1 bulky/T2 cases, finding that the LF rate was significantly lower in the CCRT group than in the RT alone group. The efficacy of CCRT in T2 laryngeal cancer was previously reported in several studies.[25,26] Overall, the low LF observed in this study may have been due to the use of CCRT for T1 bulky/T2 cases as risk groups.

The RTOG 91-11 by Forastiere et al[27] reported that use of CCRT for advanced laryngeal cancer increased the mortality rate not attributable to GC or treatments. Among the five patients who died in our study, one died from relapse, and four from secondary primary cancers; of these four patients, only one patient was treated with CCRT. There were no late AEs of grade 2 or higher in the toxicity profile of this study. The CCRT group appears to have attained good long-term results; however, longer follow-up is needed to verify the long-term effects.

In T1 bulky/T2 cases, patients who could not receive CCRT due to performance status, age, and comorbidities such as renal dysfunction were included in the RT alone group; we therefore need to explore alternative treatments to improve LC in T1 bulky/T2 patients not eligible for treatment via CCRT. We recently planned a new protocol for CCRT using S-1 (UMIN000023416) and have since started a new clinical trial.[22] Our new protocol improves the current one by reducing the S-1 administration period to 5 weeks while maintaining the daily dose, and instead changing the RT dose to 2.25 Gy/fraction for a total of 25 fractions. With these improvements, older patients may be more likely to undergo CCRT because the total S-1 dose is reduced and the hospital visit duration is shortened. However, even with this new protocol, there still are patients who are not eligible for treatment via CCRT; therefore, new treatment options need to be devised.

Twenty-two patients received CCRT with S-1, and six received CCRT with CDDP in this study; neither of these patients experienced a recurrence. Although various CCRT regimens with several antineoplastic agents have been adopted to improve the LC rate for T2 GC, their doses and schedules have not been determined. S-1 and CDDP have been reported to act as antitumor medication, as well as radiosensitizers.[28,29] S-1—an orally available antineoplastic agent—is easy to use, as patients can receive the S-1 regimen in an outpatient setting. A recent meta-analysis by Shih et al[30] reported that CCRT with S-1 for head and neck squamous cell carcinoma resulted in a good tumor response, favorable survival rate, and low number of AEs. Considering the inadequate results of our previous CCRT treatment regimen with low-dose CDDP/5-fluorouracil for T2 GC,[12,13] we prescribed high-dose CDDP for T2 unfavorable cases in this study. Forastiere et al reported the efficacy and safety of CCRT with high-dose CDDP for advanced laryngeal cancer[31]; however, the dose used in our regimen (80 mg/m^2) was lower than the one they used for advanced GC (100 mg/m^2); nevertheless, the dosing schedule was the same. Our dose reduction

is expected to be acceptable for early GC and to reduce side effects. However, additional cases are required to evaluate the efficacy and safety of our CCRT regimen with high-dose CDDP.

Limitations

Due to the retrospective nature of the study, the selection of patients based on age and comorbidities may have affected the results of the LF rate analysis when comparing the CCRT and RT alone groups. Our results seem to confirm the efficacy and safety of our original optimized treatment in early GC; however, although the number of patients in this study was greater than that in our previous report,[19] the small sample size remains a limitation of this study. We therefore need to increase the sample size over a longer duration to further investigate the efficacy and safety of our protocol.

CONCLUSION

Treating early GC according to our optimized protocol resulted in low LF rates, high OS and DSS rates, and acceptable AEs. Our results also suggest that CCRT is more effective than RT alone in T1 bulky/T2 cases.

ACKNOWLEDGMENTS

This study was possible thanks to the cooperation among many researchers. We would like to express our sincere gratitude to each of them.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1 National Cancer Institute at the National Institutes of Health. NCCN Guidelines Version 3.2021, Cancer of the Glottic Larynx. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Published 2021. Accessed May 1, 2021.

2 Forastiere AA, Ismaila N, Lewin JS, et al. Use of Larynx-Preservation Strategies in the Treatment of Laryngeal Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2018;36(11):1143–1169. doi:10.1200/JCO.2017.75.7385.

3 Cellai E, Frata P, Magrini SM, et al. Radical radiotherapy for early glottic cancer: Results in a series of 1087 patients from two Italian radiation oncology centers. I. The case of T1N0 disease. *Int J Radiat Oncol Biol Phys*. 2005;63(5):1378–1386. doi:10.1016/j.ijrobp.2005.05.018.

4 Frata P, Cellai E, Magrini SM, et al. 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(5):1387–1394. doi:10.1016/j.ijrobp.2005.05.013.

5 Mendenhall WM, Werning JW, Hinerman RW, Amdur RJ, Villaret DB. Management of T1-T2 Glottic Carcinomas. *Cancer*. 2004;100(9):1786–1792. doi:10.1002/cncr.20181.

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(5):1389–1394. doi:10.1016/j.ijrobp.2007.05.077.

7 Bhateja P, Ward MC, Hunter GH, et al. Impaired vocal cord mobility in T2N0 glottic carcinoma: Suboptimal local control with Radiation alone. *Head Neck*. 2016;38(12):1832–1836. doi:10.1002/hed.24520.

8 Harwood AR, DeBoer G. Prognostic factors in T2 glottic cancer. *Cancer*. 1980;45(5):991–995. doi:10.1002/1097-0142(19800301)45:5<991::aid-cncr2820450526>3.0.co;2-d.

9 Khan MK, Koyfman SA, Hunter GK, Reddy CA, Saxton JP. Definitive radiotherapy for early (T1-T2) glottic squamous cell carcinoma: a 20 year Cleveland Clinic experience. *Radiat Oncol*. 2012;7:193. doi:10.1186/1748-717X-7-193.

10 Kimura K, Itoh Y, Okada T, et al. Critical evaluation of a prospective study of concurrent chemoradiotherapy with S-1 for early glottic carcinoma. *Anticancer Res*. 2015;35(4):2385–2390.

11 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(1):209–213.

12 Hirasawa N, Itoh Y, Ishihara S, et al. Radiotherapy with or without chemotherapy for patients with T1-T2 glottic carcinoma: retrospective analysis. *Head Neck Oncol*. 2010;2:20. doi:10.1186/1758-3284-2-20.

13 Itoh Y, Fuwa N. Retrospective analysis: concurrent chemoradiotherapy using protracted continuous infusion of low-dose cisplatin and 5-fluorouracil for T2N0 glottic cancer. *Radiat Med*. 2006;24(4):277–281. doi:10.1007/s11604-005-1517-1.

14 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. doi:10.1200/JCO.2001.19.20.4029.

15 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(1):77–82. doi:10.1016/j.ijrobp.2005.06.014.

16 Itoh Y, Kubota S, Kawamura M, 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(4):399–406. doi:10.18999/nagjms.78.4.399.

17 Benson R, Prashanth G, Mallick S. Moderate hypofractionation for early laryngeal cancer improves local control: a systematic review and meta-analysis. *Eur Arch Otorhinolaryngol*. 2020;277(11):3149–3154. doi:10.1007/s00405-020-06012-9.

18 Itoh Y, Ono T. Proposal for personalized treatment of early glottic cancer with radiation therapy. *Nagoya J Med Sci*. 2021;83(4):663–668. doi:10.18999/nagjms.83.4.663.

19 Kimura K, Itoh Y, Okada T, et al. Optimized treatment strategy of radiotherapy for early glottic squamous cell carcinomas: an initial analysis. *Nagoya J Med Sci*. 2017;79(3):331–338. doi:10.18999/nagjms.79.3.331.

20 Union for International cancer control. Head and Neck Tumours. In: Brierley JD, Gospodarowicz MK, Wittekind Ch, eds. *TNM Classification of Malignant Tumors*. 8th ed. Chichester:Wiley-Blackwell; 2017:31–35.

21 Kanda Y. Investigation of the freely available easy-to use software 'EZR' for medical statistics. *Bone Marrow Transplant*. 2013;48(3):452–458. doi:10.1038/bmt.2012.244.

22 Kimura K, Itoh Y, Okada T, et al. Study Protocol: Prospective Study of Concurrent Chemoradiotherapy with S-1 and Hypofractionated Radiotherapy for Outpatients with Early Glottic Squamous Cell Carcinomas. *Asian Pac J Cancer Prev*. 2018;19(5):1195–1199. doi:10.22034/APJCP.2018.19.5.1195.

23 Kodaira T, Kagami Y, Shibata T, et al. Results of a multi-institutional, randomized, non-inferiority, phase III trial of accelerated fractionation versus standard fractionation in radiation therapy for T1-2N0M0 glottic cancer: Japan Clinical Oncology Group Study (JCOG0701). *Ann Oncol*. 2018;29(4):992–997. doi:10.1093/annonc/mdy036.

24 Trotti A 3rd, Zhang Q, Bentzen SM, et al. Randomized trial of hyperfractionation versus conventional fractionation in T2 squamous cell carcinoma of the vocal cord (RTOG 9512). *Int J Radiat Oncol Biol Phys*. 2014;89(5):958–963. doi:10.1016/j.ijrobp.2014.04.041.

25 Akimoto T, Nonaka T, Kitamoto Y, 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(4):995–1001. doi:10.1016/j.ijrobp.2005.10.003.

26 Nishimura G, Tsukuda M, Mikami Y, et al. Efficacy of concurrent chemoradiotherapy for T1 and T2 laryngeal squamous cell carcinoma regarding organ preservation. *Anticancer Res*. 2009;29(2):661–666.

27 Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol*. 2013;31(7):845–852. doi:10.1200/JCO.2012.43.6097.

28 Lawrence TS, Blackstock AW, McGinn C. The mechanism of action of radiosensitization of conventional chemotherapeutic agents. *Semin Radiat Oncol*. 2003;13(1):13–21. doi:10.1053/srao.2003.50002.

29 Nagasawa S, Takahashi J, Suzuki G, Hideya Y, Yamada K. Why Concurrent CDDP and Radiotherapy Has Synergistic Antitumor Effects: A Review of In Vitro Experimental and Clinical-Based Studies. *Int J Mol Sci*. 2021;22(6):3140. doi:10.3390/ijms22063140.

30 Shih HS, Jhou HJ, Ou YH, et al. The Efficacy and Adverse Events in Patients with Head and Neck Cancer Following Radiotherapy Combined with S-1 Therapy: A Meta-Analysis. *Cancers (Basel)*. 2021;13(12):2971. doi:10.3390/cancers13122971.
31 Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*. 2003;349(22):2091–2098. doi:10.1056/NEJMoa031317.