Oral Oncology 99 (2019) 104454

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Addition of S-1 to radiotherapy for treatment of T2N0 glottic cancer: Results of the multiple-center retrospective cohort study in Japan with a propensity score analysis

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ARTICLE INFO

Keywords:
T2N0 glottic cancer
S-1
Radiotherapy
Propensity score matched analysis

ABSTRACT

Objectives: This multicenter retrospective cohort study aimed to evaluate the significance of adding S-1 to radiotherapy (RT) for the treatment of T2N0 glottic cancer using a propensity score matched analysis in Japan.
Materials and Methods: This study was conducted on 287 patients with T2N0 glottic cancer who were treated with definitive RT or chemoradiotherapy with S-1 (S-1 RT) between April 2007 and March 2017. Propensity score matched analysis was performed to ensure the well-balanced characteristics of the groups of patients who received RT alone and S-1 RT. Overall, progression-free and laryngectomy-free survivals and local control and laryngeal preservation rates were compared.
Results: Fifty-four pairs of patients were selected after performing propensity score matched analysis. Clinical characteristics were well-balanced between the two groups. The overall survival of patients in the S-1 RT group was significantly better than those in the RT alone group ($P = 0.008$). The progression-free and laryngectomy-free survivals of patients in the S-1 RT group were also better than those in the RT alone group; however, the differences were not significant. In contrast, patients in the S-1 RT group had slightly lower local control and laryngeal preservation rates compared with those in the RT alone group. The incidence of dermatitis in the S-1 RT group was significantly higher than that in the RT alone group in the matched population ($P = 0.013$).
Conclusions: The addition of S-1 to RT for the treatment of T2N0 glottic cancer was not associated with better local control and laryngeal preservation rates in this study.

Introduction

Patients with early-stage (T1 or T2N0) glottic squamous cell carcinoma (SCC) generally have good prognosis with a 5-year overall survival (OS) of approximately 79–96% if they undergo curative definitive radiotherapy (RT) [1–3]. Although the treatments of choice including RT, open partial laryngectomy, and transoral surgery for patients with early glottis SCC [4] are still controversial due to the lack of strong evidence as regards their effectiveness, RT has been widely used as a curative treatment modality for patients with this disease to preserve

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https://doi.org/10.1016/j.oraloncology.2019.104454
Received 23 August 2019; Received in revised form 3 October 2019; Accepted 19 October 2019
Available online 30 October 2019

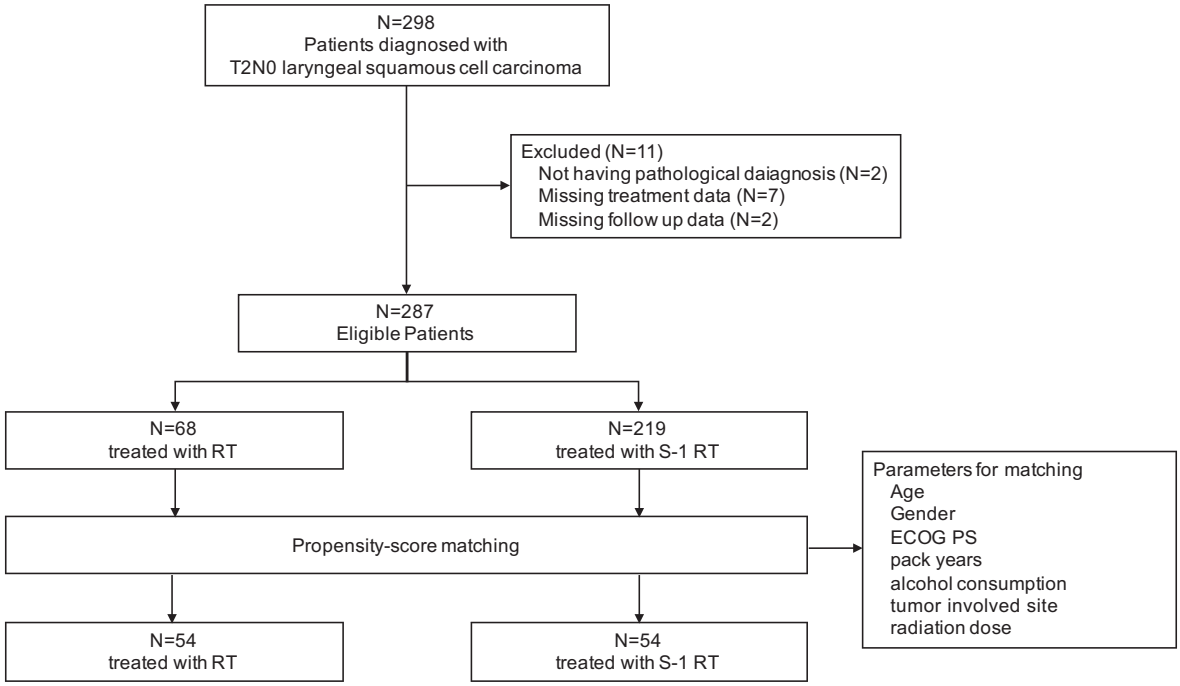

Figure 1. Patient selection flowchart. Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group performance status; RT, radiotherapy.

the larynx, maintaining the quality of the patient's voice.

RT has a high rate of locoregional control in T1 glottic SCC with a 5-year local control rate (LCR) of 82%–93%. On the contrary, the LCR for T2 glottic SCC is lower than that for T1 glottic SCC, ranging from 65% to 80% [2,3]. Generally, laryngeal tumor characteristics such as T stage classification [5] and tumor size [6] could affect the LCR by RT for patients with early-stage glottis SCC. Thus, some patients with T2 glottic SCC may have radiation failure; hence, salvage surgery including total laryngectomy is performed. Several retrospective studies conducted to assess the LCR have shown that combining chemotherapy with RT could improve the local control and larynx preservation rates of patients with early-stage glottis SCC [7–10]. In particular, S-1, an oral antitumor agent of fluorinated pyrimidines, has been widely used with RT as a treatment for patients with T2 glottic SCC in clinical practice in Japan, based on the results of the previous phase I or II studies [11–13]. However, these clinical studies were conducted with a relatively small number of patients, indicating that the significance of adding S-1 on RT to achieve better local control and laryngeal preservation rates (LPRs) compared to RT alone is still under investigation.

We therefore hypothesized that adding S-1 to RT could provide better local control, laryngeal preservation, and survival benefit for patients with T2N0 glottic SCC compared to RT alone. While we totally agree that a prospective randomized trial is the best method to examine this hypothesis, it is difficult to conduct a prospective study with larger patient population, because the 2015 version of the Report of Head and Neck Cancer Registry of Japan Clinical Statistics of Registered Patients stated that the number of newly diagnosed T2N0 glottic cancer in Japan was limited to only 367 per year [14]. We thus conducted a multicenter retrospective cohort study using a propensity score matched analysis as a realistic alternative method to test this hypothesis.

Patients and methods

Design

This is a multicenter retrospective cohort study conducted in the following 11 institutions in Kanagawa, Japan: Yokohama City University Hospital, Kanagawa Cancer Center, Kitasato University Hospital, Fujisawa City Hospital, Tokai University Hospital, Yokohama City University Medical Center, Yokohama Minami Kyosai Hospital, Yokosuka Kyosai Hospital, St. Marianna University Hospital, Showa University Fujigaoka Hospital, and Showa University Northern Yokohama Hospital. The 2015 version of the Report of Head and Neck Cancer Registry of Japan Clinical Statistics of Registered Patients stated that the number of newly diagnosed T2N0 glottic cancer was 367 per year [14]. Because the population in Kanagawa Prefecture was approximately 7% of the entire population in Japan, the incidence of T2N0 glottic cancer in Kanagawa Prefecture could be estimated as 25 per year. We assumed that, from the abovementioned 11 institutions, almost all of the patients with T2N0 glottic cancer could be recruited in this study. When the study duration was set for 10 years, we estimated that more than 250 patients could be recruited in this study. Thus, the medical records of patients with T2N0 glottic SCC who were treated with definitive RT or chemoradiotherapy with S-1 between April 2007 and March 2017 were reviewed retrospectively. This study included the results of the previous cohort of concurrent chemoradiotherapy with S-1 in patients with stage II (T2N0M0) SCC of the pharynx or larynx [10,13]. The main outcomes of this study were OS, progression-free survival (PFS), laryngectomy-free survival (LFS), LCR, and LPR. The protocol was reviewed and approved by the institutional review boards of each institution and conducted in accordance with the Declaration of Helsinki.

Patients

Patients with histologically confirmed T2 glottic SCC using the 6th or 7th edition of the AJCC/UICC TNM staging system with no evidence of cervical lymph node metastasis, of age greater than 20 years, and with adequate hematologic, renal, and hepatic function were eligible to participate. Patients who previously received chemotherapy or had synchronous multiple cancer and distant disease were excluded. Information of the following characteristics and clinical parameters were collected from the patients' records: age; sex; Eastern Cooperative Oncology Group performance status (ECOG-PS) score; primary site of laryngeal cancer; smoking history; alcohol consumption; the date of the pathological diagnosis of the disease; the date the treatment started; the

existence of past history and comorbidities; the existence of salvage surgery including total laryngectomy; the total radiation dose; the dose of S-1; adverse events including grade 3 or more (Common Terminology Criteria for Adverse Events version 3/4) blood toxicity; presence of mucositis, anorexia, diarrhea, nausea, and oral bleeding; and treatment outcomes. From the 298 patients with T2N0 glottic cancer, 11 patients were excluded for the following reasons as shown in Fig. 1; the absence of pathological diagnosis and missing treatment and follow-up data. A total of 287 patients with glottic cancer were eligible for this study. RT was performed five days a week with a single daily fraction of 1.4–2.2 Gray (Gy; mainly, 1.8 or 2.0 Gy) to a total dose of 52–74 Gy. For planning radiotherapy, 2 dimensional conventional or 3-dimentional conformal technique was used. In principle, S-1 (Taiho Pharmaceutical Co., Japan) was administrated daily for 2 weeks followed by 1 week of rest during RT. The daily dose of S-1 was considered according to the body surface area of the patients at each institution. Sixty-eight patients underwent curative RT (the RT alone group), and 219 patients underwent chemoradiotherapy with S-1 (the S-1 RT group) in this study.

Propensity score matched analysis

To reduce selection bias due to differences in patient characteristics between the RT alone and S-1 RT groups, a 1:1 ratio propensity score matched analysis was performed using a caliper width 0.2 logit of the standard deviation [15]. The propensity score was calculated using multivariate logistic regression model based on variables including age, sex, ECOG-PS score, tumor involved site, smoking history, alcohol consumption, and total dose of RT.

Statistical analysis

Chi-squared test, unpaired *t* test and Mann-Whitney test were used to examine the correlations between the categorical variables where appropriate. PFS was defined as the time of the first relapse of the disease or death from any reason, LFS as the time from diagnosis until laryngectomy or death from any cause, LCR as the time from diagnosis until local recurrence, and LPR as the time from diagnosis until laryngectomy. OS, PFS, LFS, LCR, and LPR were analyzed using the Kaplan–Meier method with the Wilcoxon log-rank test. Chi-squared test, Wilcoxon–Mann–Whitney test were then used to ensure that the variables in the two groups were well-balanced. Statistical analysis was performed using the JMP software (Version 12.2.0, SAS Institute Inc., Cary, NC), and GraphPad Prism version 6.05 (GraphPad Software, San Diego, CA). $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

The clinical characteristics of the 287 patients with glottic cancer are summarized in Table 1. The median age of patients was 69 years (range, 38–91 years), and most patients (98.6%) were male. The tumor-involved sites were the supraglottic extension in 51.6%, glottic only in 23%, subglottic extension in 22.6%, and unknown in 2.8%. A total of 82.2% of patients had ECOG-PS score of 0. The median pack-years was 40 (range, 0–150), and only 22 patients (7.7%) were never-smokers in this study. The number of patients with no experience of alcohol consumption was 35 (12.2%). A total of 234 patients remain alive without any evidence of disease, 4 died from cancer, and 25 died from causes other than cancer. Twenty patients underwent total laryngectomy as salvage surgery for disease recurrence. Sixty-eight patients underwent curative RT (the RT alone group; median dose, 70 Gy), and 219 patients underwent chemoradiotherapy with S-1 (the S-1 RT group; median dose, 70 Gy). The median daily dose of S-1 was 80 mg/body (range, 50–120 mg/body). The correlation between the clinical characteristics and treatment modalities was also examined. The original patient groups were unbalanced with significantly more old-aged patients in the RT group compared to the S-1 RT group as shown in Table 1 ($P < 0.0001$).

Table 1
Clinical characteristics of the entire patient cohort.

Clinical characteristics			All patients (N = 287)		
	All patients (N = 287)		RT alone	S-1 RT	*P* value
Median age (range, in years)	69	(38–91)	75 (54–93)	68 (39–84)	< 0.0001
Sex -N (percentage)					0.576
Male	283	98.6	68	215	
Female	4	1.4	0	4	
Tumor-involved site -N (percentage)					
Supraglottic extension	148	51.6	36	112	
Glottic only	66	23.0	15	51	
Subglottic extension	65	22.6	16	49	
Unknown	8	2.8	1	7	
PS -N (percentage)					0.101
0	236	82.2	51	185	
1	46	16.0	13	33	
2	2	0.7	2	0	
3	1	0.3	0	1	
Missing data	2	0.7	2	0	
Smoking status -N (percentage)					
Median of pack years (range)	40	0–150	40 (0–150)	40 (0–150)	0.207
Non-smoker	22	7.7	3	19	
Smoker	262	91.3	62	200	
Missing data	3	1.0	3	3	
Alcohol consumption -N (percentage)					
None	35	12.2	12	23	0.137
Occasionally	62	21.6	5	57	
Every day	129	44.9	39	90	
Unknown	51	17.8	4	47	
Missing data	10	3.5	8	2	
Median total dose of RT (range)	70	52–74	70 (60–74)	70 (52–74)	0.083
Median daily dose of S-1 (range)				80 (50–120)	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; RT, radiotherapy.

Propensity-matched patient characteristics

A propensity score matched analysis was then performed to reduce selection bias due to the differences in patient characteristics between the RT group and the S-1 RT group. After performing propensity score matched analysis, 54 pairs of patients were selected from the original 287 patients as shown in Fig. 1. In the matched population, 79 patients remain alive without any evidence of disease, and 11 died from causes other than cancer. Two patients died from cancer in this series. Nine patients underwent total laryngectomy as salvage surgery for disease recurrence (three patients in the RT alone group and six patients in the S-1 RT group). The median total dose of RT was 70 Gy (range, 60–74 Gy) in the RT alone group and 68.2 Gy (range, 60–72 Gy) in the S-1 RT group. The median daily dose of S-1 was 100 mg/body (range, 64–120 mg/body). The clinical characteristics in the propensity score matched population for treatment modalities revealed that the variables were well-balanced with low standardized differences between the two groups as shown in Table 2.

Table 2
Clinical characteristics of the propensity score-catched patients.

Clinical characteristics			Propensity-matched patients (N = 108)			
	All patients (N = 108)		RT alone	S-1 RT	*P* value	Std diff
Median age (range, in years)	74	(39–86)	74 (54–86)	74 (39–84)	0.871	0.031
Sex -N (percentage)					1	
Male	108	100.0	54	54		
Female	0	0.0	0	0		
Tumor-involved site -N (percentage)					0.571	
Supraglottic extension	53	49.1	28	25		
Glottic only	35	32.4	15	20		
Subglottic extension	19	17.6	10	9		
Unknown	1	0.9	1	0		
PS -N (percentage)					1	
0	86	79.6	43	43		
1	22	20.4	11	11		
2	0	0.0	0	0		
3	0	0.0	0	0		
Smoking status -N (percentage)						
Median of pack years (range)	44.5	0–150	40 (0–150)	50 (0–150)	0.892	0.026
Non-smoker	6	5.6	2	4		
Smoker	102	94.4	52	50		
Alcohol consumption -N (percentage)					1	
None	22	20.4	11	11		
Occasionally	14	13.0	5	9		
Every day	64	59.3	34	30		
Unknown	5	4.6	3	2		
Missing data	3	2.8	1	2		
Median total dose of RT (range)	70	60–74	70 (60–74)	68.2 (60–72)	0.821	0.044
Median daily dose of S-1 (range)				100 (64–120)		

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; RT, radiotherapy; Std diff, A standardized difference. < 0.1 suggests adequate variable balance after propensity matching.

Treatment outcome

The median follow-up duration of the overall population was 56 months (range, 2–127 months) in this study. As shown in Fig. 2A and B, the 5-year OS and PFS of all the study population were 91.3% and 81.2%, respectively. The Kaplan–Meier analysis revealed that the 5-year OS, PFS, LFS, and LCR of patients in the S-1 RT group were significantly better than those in the RT alone group (OS, 94.1% vs. 77%, $P < 0.0001$, Fig. 2C; PFS, 84.5% vs. 68.3%, $P < 0.0001$, Fig. 2D; LFS, 87.8% vs. 76.1%, $P = 0.004$, Fig. 2E; LCR, 89.5% vs. 79.5%, $P = 0.021$, Fig. 2F). On the contrary, there was no significant difference in the LPR between the S-1 RT group and the RT alone group (92.6% vs. 90.7%, $P = 0.931$, Fig. 2G).

The median follow-up duration of the propensity score matched population was 49 months (range, 2–127 months) in this study. As shown in Fig. 3A and B, the 5-year OS and PFS of the matched population were 90.5% and 75.4%, respectively, comparable to the previous results of phase II study [13]. In this series, the Kaplan–Meier analysis revealed that the 5-year OS of patients in the S-1 RT group was significantly better than those in the RT alone group as shown in Fig. 3C (95.1% vs. 83.8%, $P = 0.008$). The PFS and LFS of patients in the S-1 RT group were better than those in the RT alone group; however, the differences were not significant (PFS, 75.9% vs. 75.3%, $P = 0.331$, Fig. 3D; LFS, 84.9% vs. 78.3%, $P = 0.164$, Fig. 3E). In contrast, patients in the S-1 RT group had slightly lower 5-year LCR and LPR compared with those in the RT alone group, while the differences were not significant (LCR, 80.6% vs. 87.4%, $P = 0.695$, Fig. 3F; LPR, 88.4% vs. 93.4%, $P = 0.380$, Fig. 3G). Thus, benefit for local control and laryngeal preservation by adding S-1 on RT for patients with T2N0 glottic SCC was not observed after the propensity score matching in this study.

Lastly, acute toxicities related to the two groups in the matched patients are summarized in Table 3. Patients in the S-1 RT group experienced more dermatitis, mucositis, anorexia, diarrhea, and nausea than those in the RT alone group. In particular, the incidence of dermatitis in the S-1 RT group was significantly higher than that in the RT alone group ($P = 0.013$). Hematologic adverse events were observed in 3 of the 219 patients in the S-1 RT group, however, those patients were not included after performing propensity score matched analysis. Thus, the existence of adverse events due to chemoradiotherapy with S-1 administration was comparable to the previous results of phase II study [12,13].

Discussion

This is the first multicenter study using a propensity score matched analysis to evaluate the significance of the administration of S-1 with definitive RT in the treatment of T2N0 glottic SCC. Based on the results of the previous phase I or II studies [11–13] showing better local control and laryngeal preservation rates of chemoradiotherapy with S-1 compared to RT alone for the treatment of early glottis cancer, we postulated that this concurrent chemoradiotherapy for patients with T2N0 glottic cancer would likely show an increase in local control and laryngeal preservation rates. However, there is no evidence stating that adding S-1 to RT for the treatment of patients with T2N0 glottic SCC was associated with improved local control and laryngeal preservation in this study. Additionally, we confirmed that the administration of S-1 with RT increased the incidence of adverse effects in the treatment for T2N0 glottic cancer compared to RT alone in the present study. Thus, our results were consistent with the previous meta-analysis demonstrated by Pignon et al. stating that the benefit of adding chemotherapy to RT for early-stage SCC of the head and neck was unclear [16].

On the other hand, patients in the S-1 RT group had a significantly better OS compared with those in RT alone group in propensity score matched population in the present study. Unadjusted Kaplan–Meier curves in all population revealed that overall, progression-free and laryngectomy-free survivals in the S-1 RT group were also better than those in the RT alone group, suggesting that there might be a small portion of the population would benefit the addition of S-1 to RT in our series. As Kitani et al. previously reported, adding S-1 to RT might improve the survival of some patients by preventing distant metastasis

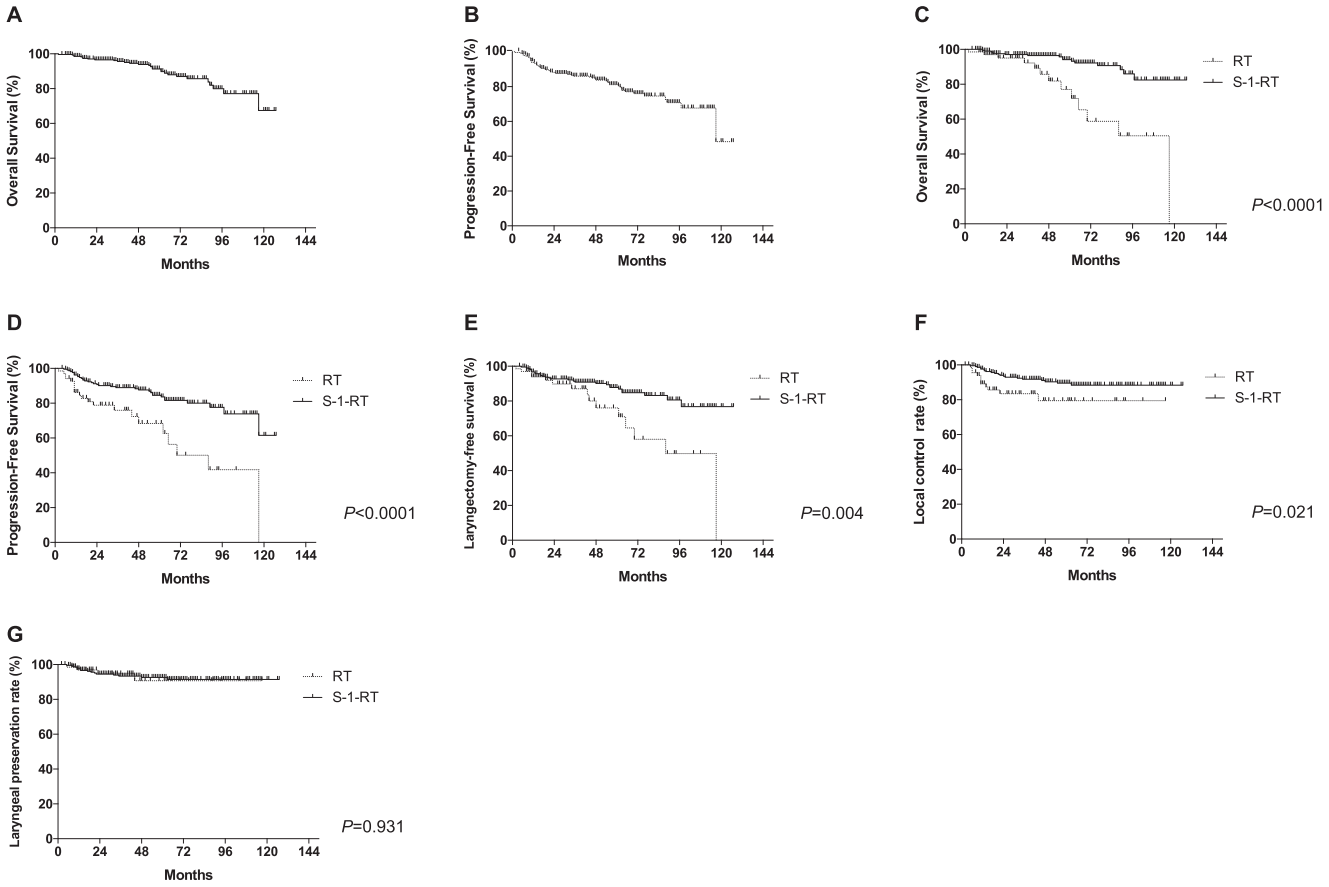

Figure 2. (A) Kaplan–Meier curves for the overall survival (OS) of patients in the overall population. (B) Kaplan–Meier curves for the progression-free survival (PFS) of patients in the overall population. (C) Unadjusted Kaplan–Meier curves for the OS of patients in the overall population. Black line, the RT alone group; dashed line, the S-1 RT group; $P < 0.0001$. (D) Unadjusted Kaplan–Meier curves for the PFS of patients in the overall population. Black line, the RT alone group; dashed line, the S-1 RT group; $P < 0.0001$. (E) Unadjusted Kaplan–Meier curves for the laryngectomy-free survival of patients in the overall population. Black line, the RT alone group; dashed line, the S-1 RT group; $P = 0.004$. (F) Unadjusted Kaplan–Meier curves for the local control rate of patients in the overall population. Black line, the RT alone group; dashed line, the S-1 RT group; $P = 0.021$. (G) Unadjusted Kaplan–Meier curves for the laryngeal preservation rate of patients in the overall population. Black line, the RT alone group; dashed line, the S-1 RT group; $P = 0.931$.

and second primary malignancies in this study, However, we need to pay attention to the possibility of bias as our study design has included the previous patients' cohort [10]. Moreover, Potential selection bias of unmeasured confounders not excluded after propensity score matching might affect the results of our analysis.

The meta-analysis by Eskiizmir et al. revealed that male patients, low hemoglobin level/anemia, T2 tumor, tumors with anterior commissure involvement, bigger tumor size/volume such as "bulky tumor," and poor differentiation/undifferentiation could be potential risk factors for radiation failure in patients with early-stage glottic SCC. Many of these factors were not evaluated in our study; however, these potential risk factors for radiation failure could affect the results of our analysis. Thus, patients with T2N0 glottic cancer with these risk factors for radiation failure might possibly benefit from concurrent chemoradiotherapy for the improvement in local control and/or laryngeal preservation rates.

There were several limitations in this retrospective observational study. First, potential selection bias cannot be excluded even after propensity score matching as mentioned above. Our dataset included unmeasured confounders such as renal function, and potential risk factors for radiation failure could affect the results of our analysis. Additionally, small number of patients, reduced to 54 in each group after propensity score matching, could also affect the results. Second, patients in this study were enrolled over a relatively long timeframe; hence, patients diagnosed with glottic cancer using both the 6th and 7th editions of the AJCC/UICC TNM staging classification were already included in this study. Third, this multicenter study could have several indications for the treatment and/or treatment procedure itself of glottic cancer, which could be considered a selection bias.

As stated in the Patients and Methods section, the number of patients with T2N0 glottic cancer, particularly accompanied with potential risk factors for radiation failure is limited, it is extremely difficult to conduct prospective randomized trials to examine the significance of the addition of S-1 to RT in patients early-stage glottic cancer with larger patient population. Therefore, although the present study had some above mentioned limitations, the lack of benefit of the addition of S-1 to RT for better local control and laryngeal preservation observed in this study could have a strong impact on the therapeutic decision for patients with early-stage glottic cancer.

Conclusion

We retrospectively compared the treatment outcomes of concurrent chemoradiotherapy with S-1 and RT alone in patients with T2N0 glottic SCC using a propensity score matched analysis. Improved overall survival was observed when S-1 was added to RT; however, our study rejected the association between adding S-1 to RT and better local control and laryngeal preservation for the treatment of T2N0 glottic SCC. Our results suggest that the addition of S-1 to RT for the treatment of patients with T2N0 glottic cancer should not be recommended for the purpose of improving the local control and laryngeal preservation.

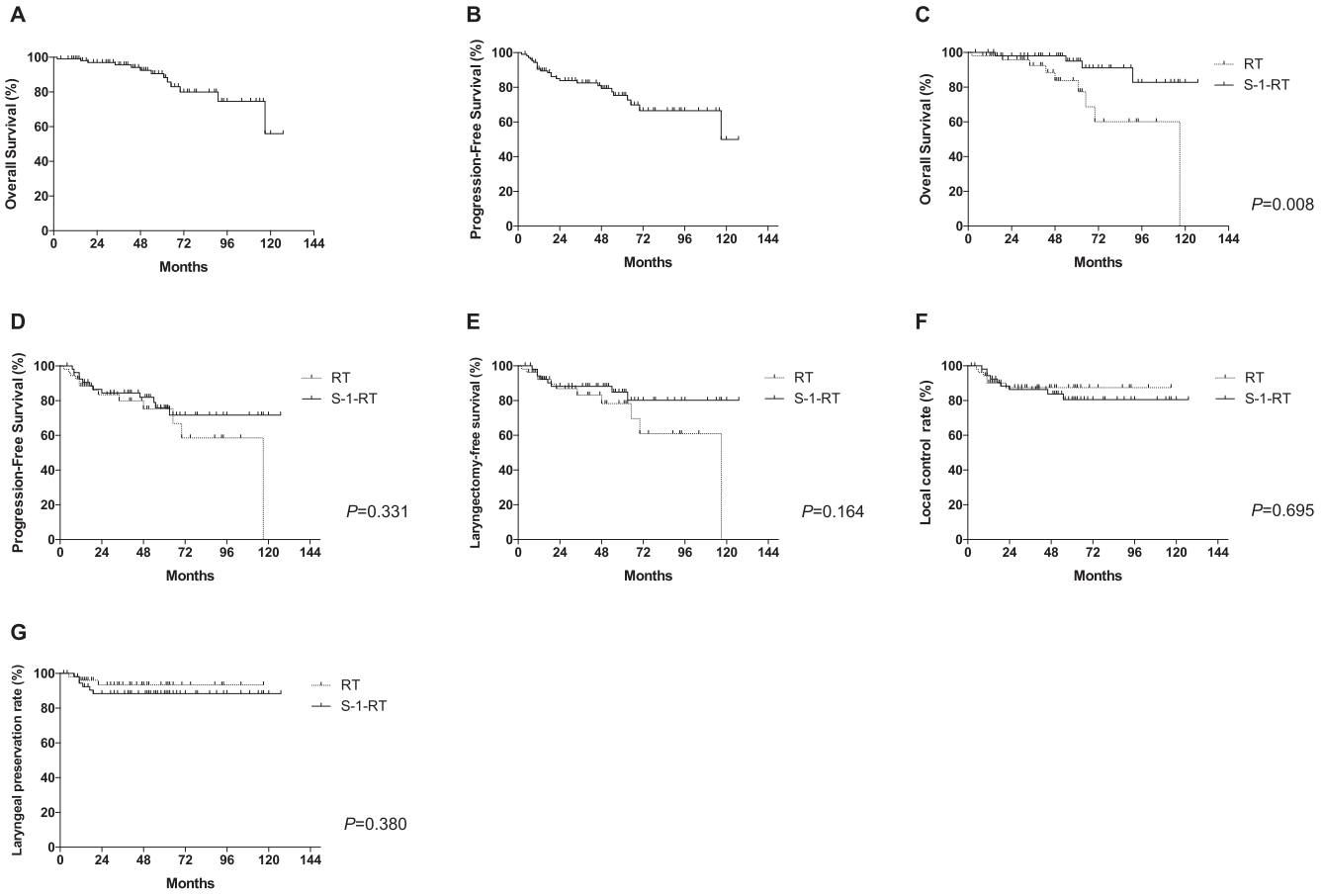

Figure 3. (A) Kaplan–Meier curves for the overall survival (OS) of patients in the matched population. (B) Kaplan–Meier curves for the progression-free survival (PFS) of patients in the matched population. (C) Adjusted Kaplan–Meier curves for the OS of patients in the matched population. Black line, the RT alone group; dashed line, the S-1 RT group; $P = 0.008$. (D) Adjusted Kaplan–Meier curves for the PFS of patients in the matched population. Black line, the RT alone group; dashed line, the S-1 RT group; $P = 0.331$. (E) Adjusted Kaplan–Meier curves for the LFS of patients in the matched population. Black line, the RT alone group; dashed line, the S-1 RT group; $P = 0.164$. (F) Adjusted Kaplan–Meier curves for the local control rate of patients in the matched population. Black line, the RT alone group; dashed line, the S-1 RT group; $P = 0.695$. (G) Adjusted Kaplan–Meier curves for the laryngeal preservation rate of patients in the matched population. Black line, the RT alone group; dashed line, the S-1 RT group; $P = 0.380$.

Table 3
Treatment-related acute adverse events.

	RT alone	S-1 RT	*P* value
Dermatitis	0	7/54 (13.0%)	0.013
Mucositis	1/54 (1.9%)	2/54 (3.7%)	1
Anorexia	0	1/54 (1.9%)	1
Diarrhea	0	2/54 (3.7%)	0.495
Nausea	0	1/54 (1.9%)	1

Abbreviations: RT, radiotherapy.

Funding

The authors received no specific support or funding for this work.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Additional Contributions: We thank Koji Ebisumoto, MD, PhD (Department of Otorhinolaryngology, Head and Neck Surgery, Tokai University Hospital, Japan); Hiroshi Hyakusoku, MD, PhD (Department of Otorhinolaryngology, Yokosuka Kyosai Hospital, Japan); Yukiko Hori, MD (Department of Head and Neck Surgery, Kanagawa Cancer Center, Japan); Yosuke Kitani, MD (Department of Otorhinolaryngology, Yokohama City University Medical Center, Japan); Takashi Wada, MD (Department of Otorhinolaryngology, Yokohama Minami Kyosai Hospital, Japan); Kaname Sato, MD, Hidetaka Ikemiyagi, MD, and Yoshihiro Aizawa, MD, (Department of Otorhinolaryngology, Head and Neck Surgery, Yokohama City University, School of Medicine, Japan), who contributed to this study. We also would like to thank Editage (www.editage.com) for English language editing.

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