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Poor local control of ulcerative T1 glottic cancer treated with 2.25-Gy per fraction radiotherapy

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ABSTRACT

The Tokai Study Group for Therapeutic Radiology and Oncology (TOSTRO) started managing T1 glottic cancer using 2.25 Gy/fraction radiotherapy in 2011. The aim was to evaluate the local control (LC) rate and toxicity with 2.25-Gy radiotherapy in clinical practice and identify prognostic factors.The eligibility criteria were T1 glottic squamous cell carcinoma patients with age ≥20 years, treated with 2.25 Gy/fraction without chemotherapy between 2011 and 2017. LC rates were evaluated based on age, performance status, sex, T-category, tumor type (ulcerative or non-ulcerative), presence of anterior commissure invasion, tumor size, X-ray beam energy, and overall treatment time. Acute and late adverse events were evaluated using CTCAE version 4.0. A total of 202 patients were enrolled. The median follow-up period was 34.2 months. The 2- and 4-year LC rates were 93.8% and 93.1%, respectively. There was a significant difference in the LC rate between non-ulcerative type and ulcerative type (95.2% vs. 74.1% at 2 years, 94.4% vs. 74.1% at 4 years; $p = 0.01$). On univariate analysis, only tumor type was significantly correlated with a poor LC rate (hazard ratio 4.3; 95% confidence interval 1.2–15.4; $p = 0.03$). Acute grade 3 adverse events occurred in 17 patients. However, no late adverse events of grade 3 or higher have occurred to date. T1 glottic cancer treatment outcomes using hypofractionated radiotherapy with 2.25 Gy/fraction in clinical practice were comparable to previously reported results. However, ulcerative type tumor was associated with a poor LC rate.

Keywords: T1 glottic cancer, hypofractionated radiotherapy, 2.25 Gy, ulcerative tumor type

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Abbreviations:
LC: local control
TOSTRO: Tokai Study Group for Therapeutic Radiology and Oncology
ACE: anterior commissure extension
PS: performance status
CR: complete clinical response
HR: hazard ratio
CI: confidence interval

INTRODUCTION

The goal of treatment for early glottic cancer is complete cure with laryngeal preservation. Therefore, definitive radiotherapy and endoscopic laser excision are generally selected as a treatment plan.

The 5-year local control (LC) rates for T1 glottic cancer treated with conventional radiotherapy have been reported to range from 73.6% to 94%.[1-12] At 10 institutions in the Tokai District, Japan, the 5-year LC rates for T1 glottic cancer treated with conventional radiotherapy alone between 2000 and 2005 were reported to be 86.5% for T1a cancer and 83.6% for T1b cancer.[8] These results are comparable to other reports.[1,7,9-11]

In 2006, a single-institution, phase III trial performed in Japan reported that hypofractionated radiotherapy using 2.25 Gy per fraction yielded a higher LC rate than did conventional radiotherapy using 2 Gy per fraction in patients with T1 glottic cancer.[9] Moreover, National Comprehensive Cancer Network clinical practice guidelines recommend either conventionally fractionated radiotherapy (66 Gy/33 fractions) or hypofractionated radiotherapy (63 Gy/28 fr) for the management of T1 glottic cancer.[13]

We, the Tokai Study Group for Therapeutic Radiology and Oncology (TOSTRO), started using definitive radiotherapy for T1 glottic cancer with 2.25 Gy per fraction in 2011 in our clinical practice, and the first report of our initial 5-year experience was published in 2016.[14]

The aim of this study was to evaluate the clinical outcomes and toxicity rates of T1 glottic cancer treated with 2.25 Gy per fraction in our clinical practice and identify the prognostic factors.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the Nagoya University Hospital (research representative facility approval: 2013-0074) and all participating institutions. After approval of the ethics committee of each participating institution, information about this study was released to the public.

Patients' characteristics

Patients treated in the TOSTRO group from January 2011 to December 2017 were collected. As the TOSTRO group, we decided to start using definitive radiotherapy for T1 glottic cancer with 2.25 Gy per fraction in 2011. Between January 2011 and November 2013, the information in Supplemental Table 1[14] was acquired from medical records retrospectively. However, after December 2013, when the ethics committees of all participating institutions approved the collection of the information shown in Supplemental Table 1, all cases were enrolled at the start

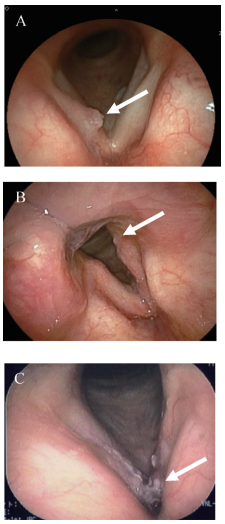

Fig. 1 Representative pictures of the following tumor types
Fig. 1A: Exophytic type.
Fig. 1B: Superficial type.
Fig. 1C: Ulcerative type, invasive lesion with erosion or ulcer on surface.

of treatment, and the information was updated annually. Eligibility criteria were age ≥20 years, T1 glottic squamous cell carcinoma patients, no chemotherapy, and treated with radiotherapy at 2.25 Gy per fraction for a total dose of approximately 63 Gy. The Eastern Cooperative Oncology Group scale was used to evaluate performance status (PS). T-category was determined according to the Union for International Cancer Control TNM classification 7th edition. The presence of anterior commissure extension (ACE) was assessed by endoscopy. Tumor type was classified by several radiation oncologists into three types, exophytic type (tumors with exophytic growth beyond the normal mucosal surface); superficial type (tumors with slight changes in mucosal surface); ulcerative type (ulcerative tumors that invades below the normal mucosal surface). Representative pictures of the three tumor types are shown in Figure 1. Localized tumor size was defined as tumor with a length <2/3 of the vocal cord, and extended tumor size was defined as tumor with a length ≥ 2/3 of the vocal cord.

Radiotherapy

All patients were placed in the supine position, immobilized with a thermoplastic mask, and treated based on three-dimensional treatment planning. The clinical target volume included the vocal cords, and the planning target volume included the clinical target volume with a sufficient margin of 5–10 mm to cover laryngeal motion (field size, approximately 5 × 5 cm). The planning target volume needed to be covered by at least 95% of the prescribed dose. A linear accelerator was used to deliver 4- or 6-MV photon beams. A standard radiation schedule was administered daily (2.25 Gy per day for a total dose of 63 Gy), five days a week. The majority of treatments were delivered using laterally opposed fields, and weighted beams and wedges were used as appropriate to improve dose homogeneity.

Outcomes

The primary response and the LC rate were diagnosed by endoscopy, and regional lymph node metastases and distant metastases were diagnosed by computed tomography and/or magnetic resonance imaging. The LC rate and overall survival were updated annually. The acute and late adverse events were evaluated using the Common Terminology Criteria for Adverse Events version 4.0. Specifically, dermatitis, laryngeal mucositis, laryngeal edema, laryngeal hemorrhage, pharyngolaryngeal pain, laryngeal necrosis, and hoarseness were evaluated.

Statistical analysis

The radiotherapy start date was the basis for determining the duration of observations. LC rates were estimated using the Kaplan-Meier method, and the log-rank test was used to assess differences in LC rates based on the following prognostic factors: age, PS, sex, T-category, tumor type, ACE, tumor size, X-ray beam energy, and overall treatment time. A Cox proportional hazards model was used for univariate analysis to determine the significance of potential risk factors for LC. Hazard ratios (HRs), 95% confidence intervals (95% CIs), and *p*-values were generated from a univariate Cox proportional hazards model. Results were considered significant at the level of $p < 0.05$, and tests were based on a two-sided significance level. Statistical computations were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

RESULTS

Included in this study were 202 patients from 11 institutions participating in TOSTRO. Of the 202 patients, 49 were treated between January 2011 and November 2013, and 153 were treated between December 2013 and December 2017. The patients' characteristics are summarized in Table 1. The median follow-up period was 34.2 (range 2.4–79.1) months. The total dose range was 56.25–67.5 Gy, and 189 patients (93.6%) received a radiotherapy dose of 63 Gy. The median duration of radiotherapy was 41 (range 33–53) days. Disease outcomes are summarized in Table 2. A complete clinical response (CR) as the primary response to treatment was observed in 201 patients (99.5%). One patient with partial response as the primary response was followed without additional treatment and is alive without evidence of recurrence. Fourteen patients (7.0%) showed local glottic recurrence during follow-up. The median time to local glottic recurrence was 14.5 (5–55) months. Eleven of these 14 patients who received salvage surgery are disease-free and alive. Three patients with recurrence did not undergo surgical salvage because of patient non-consent, old age, and complications, respectively. Twelve of the patients who showed no recurrence died of another comorbidity. There were no cases of lymph node recurrence or distant metastasis.

Table 1 Patients' characteristics (n = 202)

Characteristic	Value
Age (years), median (range)	72 (44–92)
Sex, n (%)	
Male	184 (91.1)
Female	18 (8.9)
Performance status, n (%)	
0	131 (64.9)

1	63 (31.2)
2	7 (3.5)
3	1 (0.5)
T-category, n (%)	
T1a	146 (72.3)
T1b	56 (27.7)
Anterior commissure extension, n (%)	
No	146 (72.3)
Yes	56 (27.7)
Tumor type, n (%)	
Exophytic	71 (35.1)
Superficial	119 (58.9)
Ulcerative	12 (5.9)
Tumor size, n (%)	
Localized	124 (61.4)
Extended	78 (38.6)
Energy, n (%)	
4 MV	137 (67.8)
6 MV	65(32.2)
Dose/fractions, n (%)	
56.25 Gy/25 fr	5 (2.5)
58.50 Gy/26 fr	1 (0.5)
60.75 Gy/27 fr	1 (0.5)
63.00 Gy/28 fr	189 (93.6)
67.50 Gy/30 fr	6 (3.0)

Table 2 Disease outcomes (n = 202)

Outcome	n (%)
Response	
Complete	201 (99.5)
Partial	1 (0.5)
Regional lymph node metastasis	
No	201 (99.5)
Yes	1 (0.5)
Distant metastasis	
No	202 (100)
Yes	0 (0.0)
Status	
Alive	187 (92.6)

Dead	15 (7.4)
Local glottic recurrence	
No	188 (93.1)
Yes	14 (6.9)

The 2- and 4-year LC rates for all patients were 93.8% and 93.1%, respectively (Figure 2A). The log-rank test results for prognostic factors affecting the LC rate are shown in Table 3. There was a sigificant difference in the LC rate between non-ulcerative type and ulcerative type (95.2% vs. 74.1% at 2 years, 94.4% vs. 74.1% at 4 years; p = 0.01) (Figure 2B). On univariate analysis, only tumor type correlated significantly with a poor LC rate (HR 4.3; 95% CI 1.2–15.4; p = 0.03). Acute grade 3 adverse events were observed in 17 patients (8.4%). Acute grade 3 dermatitis occurred in 13 patients (6.4%), acute grade 3 mucositis occurred in six patients (3.0%), and acute grade 3 pain occurred in one patient (0.5%). No late adverse events of grade 3 or higher have occurred to date.

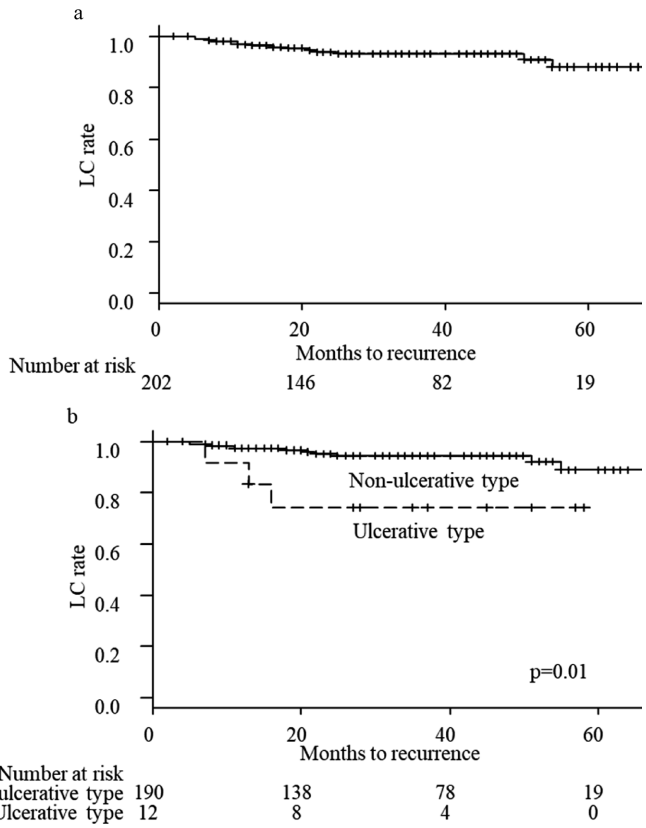

Fig. 2 Kaplan-Meier curves of local control (LC) rates
Fig. 2A: Kaplan-Meier curve of the LC rate for all patients.
Fig. 2B: Kaplan-Meier curves of LC rates for non-ulcerative type and ulcerative type.

Table 3 Prognostic factors and the LC rate

Variable	2-year LC rate	4-year LC rate	P value (log-rank)
Age, years			
<72	94.8%	94.8%	
≥72	93.2%	91.7%	0.13
Performance status			
0, 1	93.6%	92.8%	
≥2	100%	100%	0.41
Sex			
Male	93.3%	92.5%	
Female	100%	100%	0.28
T-category			
T1a	93.6%	92.6%	
T1b	94.5%	94.5%	0.79
Tumor type			
Ulcerative	74.1%	74.1%	
Non-ulcerative	95.2%	94.4%	0.01
Anterior commissure extension			
Yes	94.6%	94.6%	
No	93.7%	92.7%	0.71
Tumor size			
Localized	94.5%	93.3%	
Extended	92.8%	92.8%	0.75
X-ray beam energy, MV			
4	93.5%	92.4%	
6	94.8%	94.8%	0.85
Overall treatment time, days			
<44	95.4%	94.6%	
≥44	85.2%	85.2%	0.12

LC: local control

DISCUSSION

Several studies have reported that the risk factors for radiation failure in early glottic cancers include sex, pretreatment hemoglobin level, tobacco use, T-category, tumor size, and ACE.[15-17] However, the present analysis did not show significant differences in sex, tumor size, or ACE. Lucas et al published a systematic review and meta-analysis to assess the benefit of altered-fractionation radiotherapy in early-stage glottic cancer and reported that the benefit persisted for ACE in patients with T1 glottic cancer.[18] In addition, Tong et al reported that the negative impact of ACE could be diminished by delivering a higher tumor biological effective dose with

a fraction size > 2 Gy.[19] The present result showing no significant difference in the LC rate for ACE appears consistent with their report.

The main finding of the present study is that the ulcerative type of tumor was associated with a poor LC rate, which, to the best of the authors' knowledge, has never been reported previously. Although patients treated before December 2013 were collected retrospectively, 153 patients, accounting for approximately 3/4 of all patients, were treated from December 2013, meaning that 3/4 of all patients' tumor types were registered at the start of treatment. In addition, a subset analysis of 153 patients treated from December 2013 was performed and is shown in Supplementary Tables 2 to 4. In brief, the characteristics and disease outcomes were similar, and the LC rate of non-ulcerative type was significantly better than that of ulcerative type (94.3% vs. 64.8% at 2 years, 93.1% vs. 64.8% at 4 years; $p < 0.01$). Furthermore, on univariate analysis, ulcerative tumor type correlated significantly with a poor LC rate (HR 6.2; 95% CI 1.6–23.4; $p < 0.01$). Thus, selection bias appears to have been minimal.

Wu et al compared the surface morphology of glottic cancer with the histopathological characteristics.[20] They classified surface morphology as "pushing carcinoma" and "infiltrating carcinoma", where the morphology of infiltrating carcinoma was close to that of ulcerative type in the present analysis. They reported that infiltrating carcinoma, ulcerative type in the present classification, presented as multiple tumor nests that were often surrounded by fibrosis histopathologically. Interestingly, some authors have reported that the histological characteristics of recurrent glottic cancer after radiotherapy and primary glottic cancer are different, and most recurrent cancers present with multiple tumor nests.[21,22] The histopathology of ulcerative tumor types may be related to radiotherapy resistance, which may result in a low LC rate. Therefore, further investigation using surface morphology is desirable.

Although there have been several reports of randomized controlled trials with promising results using hypofractionation in the treatment of glottic cancer,[9,11] questions remain with respect to clinical practice. Patients with a poor PS or who are very old, and/or those with a comorbidity are often excluded from clinical trials, which may lead to different results in "real-world" practice. In the present study, there were 35 patients (17.3%) older than 80 years of age, 8 (4.0%) with PS ≥2, and 28 patients (13.9%) with a history of other malignant diseases, but they tolerated the hypofractionated treatment, and the LC rate and the adverse effects were comparable to the results from previous studies (Table 4,[3,4,8-11] Supplementary Tables 5 and 6[4,11,23,24]). Because the present study was based on clinical practice, the total dose could be increased or decreased from 63 Gy at the discretion of the clinician, considering patient age, PS, or adverse effects, and 7 patients were treated with total doses less than 63 Gy. Five patients treated with 25 fractions came from the same institution. Of the 7 patients who were treated with less than 63 Gy, all achieved CR as the primary response. One had local relapse at follow-up, but it was not ulcerative type. Six patients treated with more than 63 Gy have achieved CR to date; none had ulcerative type, and only one had acute grade 3 dermatitis. There were no grade 2 or greater late adverse events to date among patients treated with more than 63 Gy.

There are several limitations to the present study. First, the number of patients with ulcerative type was very small. Because there have been very few reports classifying tumors morphologically, the ulcerative type may be very rare. A previous study by Yamazaki et al also reported a very small number of cases of ulcerative type (2/180).[9] Therefore, additional multicenter studies are warranted. Second, the median follow-up period was relatively short to evaluate LC rates and late toxicities. However, the median time to recurrence in reported series was mostly within 30 months, and the present report was similar.[2,3,6,10-12,17,23] Late adverse events were no worse than those reported for comparable median follow-up periods.[23] Third, the pathological results of patients with local recurrence and salvage surgery were not investigated.

Table 4 Five-year LC rates from studies using hypofractionated radiotherapy with 2.25 Gy for T1 glottic cancer

Author	Dose/fractions	Fraction size (Gy)	LC rate, T1a	LC rate, T1b	LC rate, all T1
Current study (TOSTRO Study)	63 Gy/28 fr (6% of series included other schedules)	2.25	92.6% (4-year LC rate)	94.5% (4-year LC rate)	93.1% (4-year LC rate)
Hirasawa et al[8] (TOSTRO Study)	60–74 Gy/30–37 fr (9% of series included other schedules)	2	86.5%	83.8%	
Yamazaki et al[9] (RCT)	56.25–63 Gy/25–28 fr, 60–66 Gy/30–33 fr	2.25, 2			92%, 77%
Moon et al[11] (RCT)	63 Gy/28 fr, 66 Gy/33 fr	2.25, 2	93.0%, 76.7%	83.2%, 87.6%	90.1%, 80.3%
Kim et al[3]	67.5 Gy/30 fr, 70 Gy/35 fr	2.25, 2			95%, 83%
Chera et al[10]	63 Gy/28 fr (39% of series included other schedules)	2.25	94%	93%	
Salas et al[4]	63.8–63 Gy/22–29 fr, 70 Gy/35 fr	2.2–2.25, 2			83.7%, 86.2%

RCT: randomized, controlled trial
LC: local control

CONCLUSION

TOSTRO's LC rates for T1 glottic cancer treated using 2.25 Gy per fraction in practice were better than those using 2 Gy per fraction from 2000 to 2005.8 However, the ulcerative type of tumor was associated with a poor LC rate; thus, further investigation of this tumor subtype is warranted.

CONFLICT OF INTEREST

None.

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Appendix.

Supplementary Table 1 Questionnaire summary[14]

Questionnaire items
1. Age, sex, performance status (Eastern Cooperative Oncology Group)
2. T- category: T1a/T1b
3. Tumor type: exophytic/superficial/ulcerative
4. Anterior commissure extension
5. Tumor size: localized (<2/3 of the vocal cord) / extended (≥2/3 of the vocal cord)
6. Radiation starting date, ending date, break period
7. X-ray beam energy, dose fractionation, total radiation dose
8. Primary response, local control
9. Regional lymph node metastases, distal metastases
10. Life and death, date last verified
11. Acute and late adverse events (Common Terminology Criteria for Adverse Events version 4.0)

Supplementary Table 2 Patients' characteristics (n = 153)

Characteristic	Value
Age (years), median (range)	72 (44–92)
Sex, n (%)	
Male	137 (89.5)
Female	16 (10.5)
Performance status, n (%)	
0	104 (68.0)
1	45 (29.4)
2	3 (2.0)
3	1 (0.7)
T-category, n (%)	
T1a	107 (69.9)
T1b	46 (30.1)
Anterior commissure extension, n (%)	
No	106 (69.3)
Yes	47 (30.7)
Tumor type, n (%)	
Exophytic	88 (57.5)
Superficial	56 (36.6)
Ulcerative	9 (5.9)
Tumor size, n (%)	
Localized	95 (62.1)

Extended	58 (37.9)
Energy, n (%)	
4 MV	106 (69.3)
6 MV	47 (30.7)
Dose/fractions, n (%)	
56.25 Gy/25 fr	3 (2.0)
58.50 Gy/26 fr	1 (0.7)
60.75 Gy/27 fr	1 (0.7)
63.00 Gy/28 fr	142 (92.8)
67.50 Gy/30 fr	6 (3.9)

Supplementary Table 3 Disease outcomes (n = 153)

Outcome	n (%)
Response	
Complete	153 (100)
Partial	0 (0)
Regional lymph node metastasis	
No	153 (100)
Yes	0 (0)
Distant metastasis	
No	153 (100)
Yes	0 (0)
Status	
Alive	146 (95.4)
Dead	7 (4.6)
Local glottic recurrence	
No	142 (92.8)
Yes	11 (7.2)

Supplementary Table 4 Prognostic factors and the LC rate (n = 153)

Variable	2-year LC rate	4-year LC rate	P value (log-rank)
Age, years			
<72	94.4%	94.4%	
≥72	91.0%	88.7%	0.15
Performance status			
0, 1	92.2%	91.0%	
≥2	100%	100%	0.54
Sex			
Male	91.6%	90.4%	
Female	100%	100%	0.27
T-category			
T1a	92.1%	90.5%	
T1b	93.2%	93.2%	0.88
Tumor type			
Ulcerative	64.8%	64.8%	
Non-ulcerative	94.3%	93.1%	< 0.01
Anterior commissure extension			
Yes	93.5%	93.5%	
No	92.1%	90.6%	0.87
Tumor size			
Localized	93.9%	92.1%	
Extended	90.0%	90%	0.62
X-ray beam energy, MV			
4	91.3%	89.8%	
6	95.6%	95.6%	0.43
Overall treatment time, days			
<44	93.6%	92.3%	
≥44	86.5%	86.5%	0.34

LC: local control

Supplementary Table 5 Grade ≥3 acute AEs from studies using hypofractionated radiotherapy

	Acute AE	CONV, N (%)		HYPO, N (%)	
		Grade 3	Grade 4	Grade 3	Grade 4
Current study N=202	Dermatitis			13 (6.4)	0 (0)
	Laryngeal mucositis			6 (3.0)	0 (0)
	Laryngeal edema			0 (0)	0 (0)
	Laryngeal hemorrhage			0 (0)	0 (0)
	Pharyngolaryngeal pain			1 (0.5)	0 (0)
Moon et al[11] (RCT) CONV, N=82 HYPO (2.25 Gy), N=74	Skin	0 (0)	0 (0)	0 (0)	0 (0)
	Mucosa	0 (0)	0 (0)	0 (0)	0 (0)
	Larynx	0 (0)	0 (0)	0 (0)	0 (0)
Salas et al[4] CONV, N=71 HYPO (2.2–2.25 Gy), N=67	Skin	1 (1.4)	0 (0)	4 (6.0)	0 (0)
	Mucosa	5 (7.0)	0 (0)	4 (6.0)	0 (0)
	Larynx	1 (1.4)	0 (0)	1 (1.5)	0 (0)
Vassikis et al[23] HYPO (2.3 Gy), N=47	Whispered speech			4 (8.5)	0 (0)
	Throat pain or referred ear pain requiring narcotic				
	Confluent fibrinous exudate				
	Marked arytenoid edema				
Kodaira et al[24] (RCT) CONV, N=177 HYPO (2.4 Gy), N=183	Skin	18 (10.2)	0 (0)	7 (3.8)	0 (0)
	Mucosa	7 (4)	0 (0)	10 (5.5)	0 (0)
	Pain	0 (0)	0 (0)	0 (0)	0 (0)
	Dysphagia	0 (0)	0 (0)	0 (0)	0 (0)
	Voice Change	2 (1.1)	0 (0)	4 (2.2)	0 (0)

AE: adverse event
CONV: conventional radiotherapy
HYPO: hypofractionated radiotherapy
RCT: randomized, controlled study

Supplementary Table 6 Grade ≥3 late AEs from studies using hypofractionated radiotherapy

	Late AE	CONV, N (%)		HYPO, N (%)	
		Grade 3	Grade 4	Grade 3	Grade 4
Current study N=202	Hoarseness			0 (0)	0 (0)
	Laryngeal necrosis			0 (0)	0 (0)
	Laryngeal edema			0 (0)	0 (0)
	Laryngeal hemorrhage			0 (0)	0 (0)
	Pharyngolaryngeal pain			0 (0)	0 (0)
Moon et al[11] (RCT) CONV, N=82 HYPO (2.25 Gy), N=74	Skin	0 (0)	0 (0)	0 (0)	0 (0)
	Mucosa	0 (0)	0 (0)	0 (0)	0 (0)
	Larynx	0 (0)	0 (0)	0 (0)	0 (0)
Salas et al[4] CONV, N=71 HYPO (2.2–2.25 Gy), N=67	Larynx	1 (1.4)	0 (0)	1 (1.5)	0 (0)
Vassikis et al[23] HYPO (2.3 Gy), N=47	Laryngeal edema			0 (0)	0 (0)
	Chondritis				
Kodaira et al[24] (RCT) CONV, N=182 HYPO (2.4 Gy), N=184	Laryngeal edema	0 (0)	0 (0)	0 (0)	0 (0)
	Pharyngolaryngeal pain	1 (0.5)	0 (0)	1 (0.5)	0 (0)
	Voice change	0 (0)	0 (0)	0 (0)	0 (0)
	Soft tissue necrosis	0 (0)	1 (0.6)	1 (0.6)	1 (0.6)
	Induration	0 (0	–	0 (0)	0 (0)

AE: adverse event
CONV: conventional radiotherapy
HYPO: hypofractionated radiotherapy
RCT: randomized, controlled study