Predictive factors for local control of early glottic squamous cell carcinomas after definitive radiotherapy

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Received September 11, 2019; Accepted January 29, 2020

DOI: 10.3892/mco.2020.2024

Abstract. The aim of the present study was to retrospectively investigate the risk factors of local failure for T1 glottic carcinoma irradiated with a prescription dose of 66 Gy. Between July 2006 and December 2017, 64 patients with T1 glottic squamous cell carcinoma treated with 66 Gy/33 fractions were analyzed for risk factors of local failure. The sex, age, performance status, T stage, overall treatment time, anterior commissure involvement, smoking status during/after treatment, histological tumor grade and pretreatment hemoglobin level were investigated. The maximum, mean and minimum doses, and the homogeneity index for the glottic larynx were calculated for dosimetric risk factors of local failure. The median follow-up duration was 51 months. Local failure was observed in 6 patients (9.5%). Among all risk factors, only the minimum dose to the glottic larynx was found to be significantly associated with local failure (P=0.025). The 5-year local control rates for a minimum dose to the glottic larynx of <65 and ≥65 Gy were 79 and 95%, respectively, with a statistically significant difference (P=0.015). No patients exhibited grade ≥3 late adverse effects. The minimum dose to the glottic larynx was the only factor significantly associated with local failure. Thus, local control of T1 glottic carcinoma may improve with a minimum dose of ≥65 Gy to the glottic larynx. In conclusion, radiotherapy with a minimum prescription dose of ≥65 Gy to the glottic larynx appears to be safe and achieves a high local control rate for T1 glottic carcinoma.

Introduction

Radiotherapy (RT) is a well-established treatment modality for patients with early laryngeal carcinoma; however, laser therapy and partial laryngectomy may also be used to definitively treat early laryngeal carcinomas (1-3). The goals of treatment are cancer cure, preservation of the vocal cords with acceptable voice quality, and minimal treatment-related mortality. Definitive RT may achieve all these goals in the majority of patients with early laryngeal carcinoma, and salvage laryngectomy may be effective in cases of relapse. The local control rate for patients with early laryngeal carcinoma who undergo salvage laryngectomy for recurrence after initial RT is 90-100% (4-9).

Laryngeal carcinoma is classified into glottic, supraglottic and subglottic types according to the place of origin, with glottic carcinomas being the most common (70%). The majority of glottic carcinomas are at an early stage and account for ~70% of all cases. The most commonly used dose-fractionation schedule for T1 glottic carcinoma is 66 Gy/33 fractions. The local control rate for T1N0 glottic carcinoma treated with conventional fractionation is 80-90% (8,10-12). Thus, RT alone results in an adequate local control rate for T1 glottic lesions, with a low incidence rate of severe complications. However, some patients may experience local failure. The local control rate for T1 glottic carcinoma may be improved by identifying the risk factors for local failure. Therefore, the aim of the present study was to retrospectively investigate the risk factors of local failure in patients with T1 glottic carcinoma irradiated with a prescription dose of 66 Gy.

Patients and methods

Patients. Between July 2006 and December 2017, 69 consecutive patients with early (T1) glottic squamous cell carcinoma were treated with definitive RT. All patients provided written informed consent, and the study was approved by the Ethics Review Board of the Tokyo Medical University Hospital (Tokyo, Japan). Among the 69 patients, 64 who underwent irradiation with a dose-fractionation schedule of 66 Gy/33 fractions were selected for the retrospective analysis. The characteristics of the 64 patients are listed in Table I. Tumor stage was defined according to the 2016 TNM classification (13) (8th edition, International Union Against Cancer). Of the 64 patients, 57 were men and 7 were women. The median patient age was 72 years (range, 47-86 years). A total of 98% of the patients had an Eastern Cooperative Oncology Group performance status score of 0 or 1. The primary tumor stage

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Key words: predictive factors, early glottic carcinoma, definitive radiotherapy, local control, clinical risk factor, dosimetric risk factors

Table I. Patient and tumor characteristics (n=64).

Characteristics	No. (%)
Sex	
Male	57 (89)
Female	7 (11)
Age, years [median (range)]	72 (47-86)
Performance status score	
0	60
1	3
2	0
3	1
Stage of primary tumors	
T1a	43 (67)
T1b	21 (33)
Smoking during/after treatment	
Yes	28 (44)
No	36 (56)
Anterior commissure involvement by tumor	
Yes	23 (36)
No	41 (64)
Histological grade	
Well-differentiated	45 (70)
Moderately/poorly differentiated	19 (30)
Pretreatment hemoglobin level, g/dl	
≤14	25 (39)
>14	39 (61)

was T1a in 43 and T1b in 21 patients. None of the patients had clinical neck or distant metastasis. Among the 64 patients, 55 experienced hoarseness. In addition, 15 patients (23%) had double cancers, 4 (6%) had triple cancers, and 2 (3%) had quadruple cancers, including the glottic tumor.

RT. Three-dimensional RT was planned and performed using a shell with the patient placed in the supine position. For treatment planning, all patients underwent cervical computed tomography (CT) with a 2.5 mm slice thickness. Treatment planning was performed using the Eclipse™ (Varian Medical Systems) treatment planning system. The standard RT technique involved parallel opposing lateral fields using photons of 4-MV X-rays for all patients over 5 days per week. The volume of the glottic larynx was defined as the vocal cord and was contoured by a single radiation oncologist. The gross tumor volume was defined based on endoscopy findings. However, it was not delineated in the present study, owing to non-visualization on CT and magnetic resonance imaging. The clinical target volume (CTV) encompassed the glottis, subglottis and part of the supraglottis; cranially and anteriorly, the CTV extended to the thyroid notch at the level of the vocal process of the arytenoid cartilage, and caudally and posteriorly it extended to the middle of the cricoid cartilage. A 5 mm isotropic expansion of the CTV provided the planning target volume (PTV). A typical contouring of the target volume and beam's eye view are shown in Fig. 1. Irradiation was delivered via local portals (mostly 5-6x5-6 cm) covering only the primary lesion. The cervical lymph nodes were not electively treated. The dose and fractionation for all patients was 66 Gy/33 fractions delivered over 6.6 weeks.

Evaluation of local response and adverse effects. The local response was evaluated by laryngoscopy at 1 month after completion of RT. In the absence of clinical symptoms, regular follow-up visits were performed at 2-3-month intervals for the first 2 years, and every 4-6 months thereafter. At each follow-up visit, the evaluation included laryngoscopy, medical history taking, physical examination, CT, and tumor marker assessment. The data pertaining to adverse effects were collected retrospectively from patient files. Local failure was considered to occur when local recurrence developed after an initial complete response. The Common Terminology Criteria for Adverse Events (14), version 3.0 (CTCAE v3.0) were used for evaluating the acute and late effects of RT.

Risk factors for local failure. The following factors were investigated to determine the clinical risk factors for local failure: Sex, age, performance status, T stage, overall treatment time (OTT), anterior commissure involvement (ACI), smoking status during/after treatment, histological tumor grade, and pretreatment hemoglobin levels. The pretreatment hemoglobin level was measured within 1 month prior to the initiation of RT. The maximum, mean and minimum doses and the homogeneity index (HI) for the glottic larynx, CTV and PTV were evaluated as dosimetric risk factors for local failure. The HI was calculated as the maximum dose divided by the minimum dose to the target volume (15).

Statistical analysis. The endpoint was local control, calculated from the first date of RT. The associations between local failure and the clinical factors were calculated using the Fisher's exact probability test. The associations between local failure and dosimetric factors were analyzed using the Mann-Whitney U test. The local control rate was plotted using the Kaplan-Meier method, with statistical significance assessed by the log-rank test. Univariate logistic regression analyses were performed to evaluate the data using SPSS 20.0 (IBM Corp.). Differences with P-values <0.05 were considered statistically significant.

Results

Local control and overall survival. The median follow-up duration was 51 months (range, 4-132 months). All patients with local failure of the primary lesion treatment who were successfully salvaged by surgery were considered to have had local failure with RT. The overall survival and local control curves are shown in Figs. 2 and 3. The 5-year overall survival rate was 96%, and 2 (3.1%) of the 64 cases died from gastric cancer and pneumonia. The 5-year local control rate was 92%, and local failure was observed in 6 (9.5%) of the 64 cases; local failure alone occurred in 5 patients, whereas local failure and neck metastasis occurred in 1 patient. The median time for local failure was 12 months (range, 2-94 months) after the start of RT.

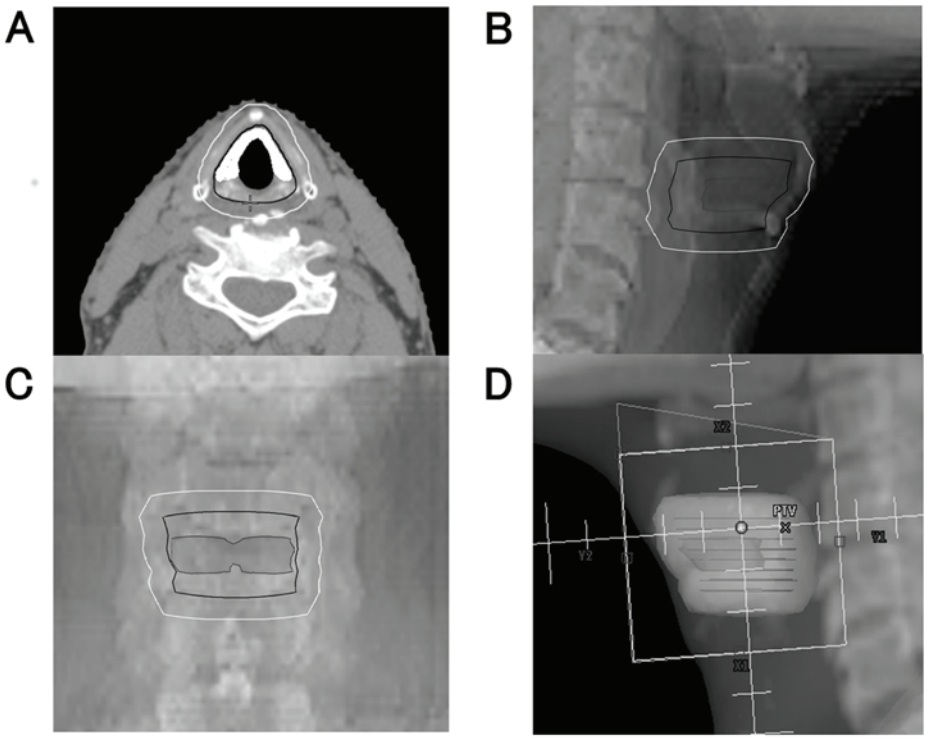

Figure 1. Typical contouring of the target volume and beam's eye view. (A) CT image for RT planning. The full white, black line and white line show the glottic larynx, CTV and PTV, respectively. (B and C) Sagittal and coronal tomography images for RT planning. (D) Beam's eye view of the typical field for RT planning. CT, computed tomography; RT, radiotherapy; CTV, clinical target volume; PTV, planning target volume.

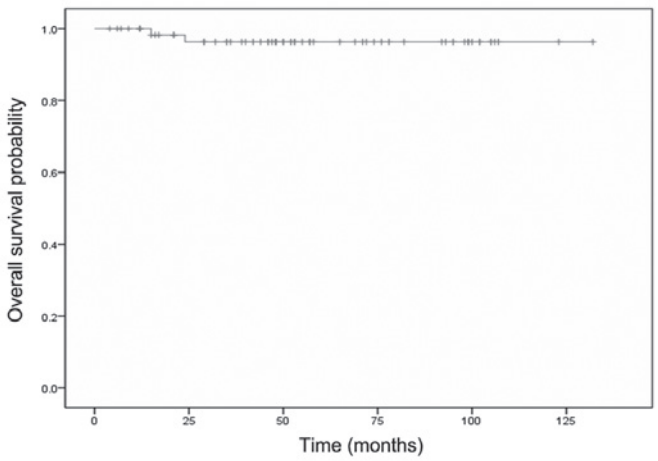

Figure 2. Overall survival curve. The 5-year overall survival rate was 96%, and 2 (3.1%) of the 64 patients died from other causes.

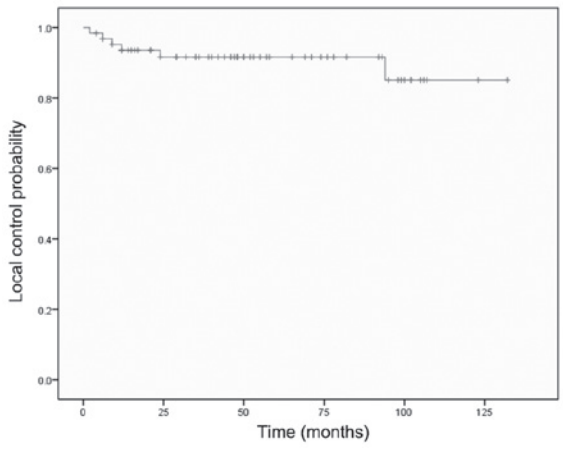

Figure 3. Local control curve. The 5-year local control rate was 92%, and local failure was observed in 6 (9.5%) of the 64 cases; local failure alone occurred in 5 patients and local failure with neck metastasis occurred in 1 patient.

The associations between the clinical factors and local failure are summarized in Table II. No factor exhibited a significant association. Multivariate analysis was not performed owing to the limited data. The associations between the dosimetric factors and local failure in all the patients are shown in Table III. On univariate analysis, the minimum dose to the glottic larynx, calculated using Mann-Whitney U test, was the only factor significantly associated with the occurrence of local failure (P=0.025). The median minimum dose to the glottic larynx was ~65 Gy. The 5-year local control rates for patients with minimum doses to the glottic larynx of <65 and ≥65 Gy were 79 and 95%, respectively (Fig. 4). The difference in the local control rate between patients who received <65 and ≥65 Gy as the minimum dose to the glottic larynx, calculated using the log-rank test, was statistically significant (P=0.015).

Adverse effects. The acute and late adverse effects of RT are shown in Table IV. Of the 64 patients, 16 (25%) had grade 2 acute dermatitis and 2 (3%) had grade 3 acute dermatitis. Although 28 patients (44%) had grade 2 acute mucositis, none demonstrated acute adverse effects or late adverse effects of grade ≥3.

The clinical data and dosimetric factors for all cases are listed in Tables V and VI.

Table II. Clinical risk factors associated with local failure.

Risk factors	Local failure, n=6	Univariate analysis	
		P-value	Hazard ratio (95% CI)
Sex (male vs. female)	11% (6/57) vs. 0% (0/7)	>0.999	Uncomputable
Age, years (<75 vs. ≥75)	10% (4/39) vs. 8% (2/25)	>0.999	0.837 (0.086-8.106)
PS score (0 vs. ≥1)	10% (6/60) vs. 0% (0/4)	>0.999	Uncomputable
T stage (T1a vs. T1b)	12% (5/43) vs. 5% (1/21)	0.654	3.481 (0.282-42.978)
OTT (≤49 vs. >49)	11% (6/56) vs. 0% (0/8)	>0.999	Uncomputable
ACI (yes vs. no)	9% (2/23) vs. 10% (4/41)	>0.999	1.622 (0.231-11.395)
Smoking during/after treatment (yes vs. no)	11% (3/28) vs. 8% (3/36)	>0.999	1.109 (0.141-8.708)
Histological tumor grade (well vs. moderately/poorly differentiated)	7% (3/45) vs. 16% (3/19)	0.351	0.567 (0.099-3.251)
Pretreatment hemoglobin level, g/dl (≤14 vs. >14)	4% (1/25) vs. 13% (5/39)	0.391	1.273 (0.107-15.196)

PS, performance status; OTT, overall treatment time; ACI, anterior commissure involvement; CI, confidence interval.

Table III. Association between dosimetric factors and local failure.

Dose, Gy	Local failure		P-value
	Yes	No	
Glottic larynx			
Max dose	69.0 (66.6-71.8)	69.0 (66.6-71.8)	0.613
Mean dose	66.7 (65.6-68.4)	67.1 (64.9-69.9)	0.478
Min dose	64.6 (64.2-65.4)	65.6 (62.7-69.4)	0.025
HI	1.06 (1.02-1.09)	1.04 (1.00-1.08)	0.053
CTV			
Max dose	68.8 (66.2-71.1)	68.8 (66.5-71.8)	0.920
Mean dose	65.7 (65.0-66.9)	65.8 (64.6-68.9)	0.506
Min dose	62.3 (61.1-62.7)	62.1 (52.1-66.6)	0.728
HI	1.11 (1.06-1.14)	1.11 (1.04-1.34)	0.728
PTV			
Max dose	69.0 (66.5-71.1)	68.9 (66.6-71.8)	0.991
Mean dose	65.4 (64.5-66.2)	65.3 (63.8-68.0)	0.866
Min dose	52.1 (22.9-57.8)	40.4 (8.9-60.5)	0.122
HI	1.34 (1.15-3.09)	1.69 (1.11-7.88)	0.106

Doses are presented as mean (range). HI, homogeneity index; CTV, clinical target volume; PTV, planning target volume.

Table IV. Acute and late radiation-related toxicities.

Toxicities	Grade			
	0 or 1	2	3	4
Acute				
Dermatitis	46	16	2	0
Mucositis	36	28	0	0
Late				
Laryngeal edema	64	0	0	0
Dermatitis	64	0	0	0
Myelopathy	64	0	0	0

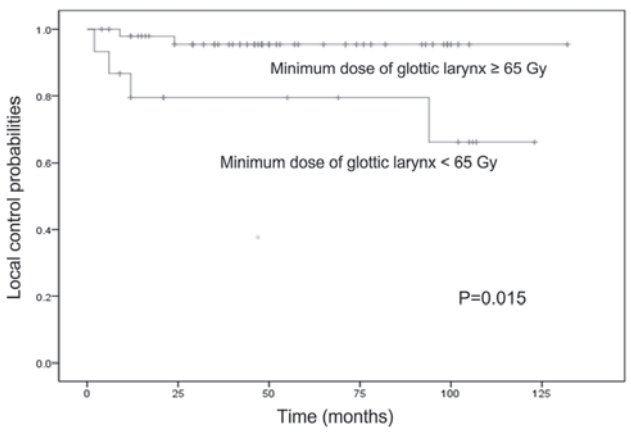

Figure 4. The 5-year local control rates for patients with minimum doses to the glottic larynx of <65 and ≥65 Gy were 79 and 95%, respectively. The difference was considered as statistically significant (P=0.015).

Discussion

In the present study, the 5-year local control rates for T1 glottic carcinomas treated with minimum doses of <65 and ≥65 Gy to the glottic larynx were 79 and 95%, respectively. The difference in the local control rate between patients treated with minimum doses of <65 and ≥65 Gy to the glottic larynx was statistically significant (P=0.015).

Several previous studies have reported on the risk factors for local failure in patients with T1 glottic carcinoma. The

Table V. Clinical risk factors for local failure in all cases.

No.	Age, years	Sex	PS score	T stage	OTT (days)	ACI (yes vs. no)	Smoking (yes vs. no)	Histological tumor grade (well vs. moderate/poorly differentiated)	Pretreatment hemoglobin (g/dl)
1	52	M	0	1a	45	Yes	Yes	Well	14.6
2	73	M	0	1b	46	Yes	Yes	Well	15
3	65	M	0	1b	50	Yes	Yes	Well	14.8
4	80	M	0	1a	45	Yes	No	Well	14.4
5	79	M	0	1a	47	No	No	Well	15.6
6	77	F	0	1b	45	Yes	No	Well	11
7	57	M	0	1a	44	No	Yes	Moderate-poor	15.7
8	83	M	0	1b	45	Yes	No	Well	15.4
9	65	F	0	1a	45	No	No	Moderate-poor	14.5
10	55	F	0	1a	47	Yes	No	Well	13
11	75	M	0	1a	44	No	No	Well	13.2
12	63	M	0	1b	44	Yes	No	Well	15.5
13	58	F	0	1a	39	No	No	Well	14.5
14	47	M	0	1a	50	No	Yes	Well	14
15	71	M	3	1a	46	Yes	Yes	Moderate-poor	11.3
16	72	M	0	1b	49	No	No	Well	14.7
17	73	M	0	1a	44	No	Yes	Moderate-poor	15.9
18	76	M	0	1a	47	No	No	Moderate-poor	14.9
19	64	M	0	1a	51	No	Yes	Well	15.6
20	71	M	0	1a	45	No	Yes	Moderate-poor	14.8
21	73	M	0	1b	50	No	Yes	Well	12.4
22	76	M	0	1a	50	Yes	No	Well	14.5
23	84	M	0	1a	45	No	No	Well	14.3
24	70	M	0	1a	45	No	No	Moderate-poor	16.5
25	65	M	0	1b	44	No	Yes	Well	13.6
26	70	M	0	1a	47	No	Yes	Well	15.9
27	73	M	0	1a	43	No	No	Well	10.6
28	70	M	0	1a	44	No	Yes	Moderate-poor	15.1
29	82	M	0	1a	45	No	No	Moderate-poor	14.3
30	65	M	0	1b	46	Yes	No	Well	14.4
31	58	M	0	1a	43	No	Yes	Well	14.2
32	64	M	0	1b	45	Yes	No	Moderate-poor	14
33	69	M	0	1a	46	No	Yes	Well	13.6
34	75	M	0	1a	46	No	No	Moderate-poor	14.4
35	70	M	0	1a	45	Yes	Yes	Moderate-poor	14.8
36	73	M	0	1b	46	Yes	No	Well	18
37	86	M	1	1a	49	No	No	Well	15
38	81	M	0	1a	48	No	No	Well	12.4
39	80	M	0	1b	44	yes	No	Well	13.6
40	86	M	0	1a	46	No	No	Well	12.4
41	70	M	0	1b	44	No	No	Well	15.9
42	84	M	0	1a	50	No	No	Moderate-poor	13.3
43	63	F	0	1a	49	No	Yes	Well	13.2
44	70	M	0	1a	44	No	No	Well	15
45	77	M	0	1a	48	No	No	Well	14
46	79	M	0	1a	49	No	Yes	Well	12.6
47	64	F	0	1a	52	No	No	Well	13.6
48	66	M	0	1a	51	Yes	Yes	Well	15.5
49	84	M	0	1a	44	Yes	No	Well	15.2

Table V. Continued.

No.	Age, years	Sex	PS score	T stage	OTT (days)	ACI (yes vs. no)	Smoking (yes vs. no)	Histological tumor grade (well vs. moderate/ poorly differentiated)	Pretreatment hemoglobin (g/dl)
50	84	M	1	1a	44	No	No	Moderate-poor	11
51	85	M	0	1b	45	Yes	No	Well	13.6
52	72	M	0	1b	48	Yes	Yes	Moderate-poor	14.9
53	72	M	0	1b	45	No	Yes	Well	12.5
54	66	M	0	1b	44	No	Yes	Moderate-poor	15.4
55	80	F	0	1a	45	No	No	Well	13.8
56	83	M	0	1b	44	No	No	Well	12.1
57	67	M	0	1a	44	Yes	No	Moderate-poor	16.6
58	73	M	0	1a	45	No	Yes	Well	15.8
59	84	M	0	1b	49	Yes	No	Moderate-poor	13.4
60	71	M	0	1a	44	No	Yes	Well	16.2
61	84	M	1	1a	45	No	Yes	Moderate-poor	14.8
62	70	M	0	1b	45	Yes	Yes	Well	14.2
63	76	M	0	1a	48	No	Yes	Well	14.3
64	68	M	0	1b	48	Yes	Yes	Well	13.6

OTT, overall treatment time; ACI, anterior commissure involvement; M, male; F, female; PS, performance status.

local control rate for Tl tumors with an overall treatment time of 42-49 days was previously reported to be significantly higher compared with that of tumors with corresponding treatment times of >49 days (P<0.02) (11). In addition, previous studies have demonstrated an association between low hemoglobin levels and poor local control, i.e., pre-treatment anemia was an adverse factor for survival in patients with early-stage glottic carcinoma (16,17); this was not observed in the present study. There was a significant decrease in the 10-year overall survival rate in patients with pre-RT anemia compared with those without pre-RT anemia (52 vs. 68%, respectively) (18). Furthermore, a recent systematic review and meta-analysis was performed to determine the risk factors for RT failure in early-stage glottic carcinoma (19). There was a higher risk of RT failure in male patients [relative risk (RR)=0.927, P<0.001], patients with low hemoglobin levels (RR=0.891, P<0.001), tumors with ACI (RR=0.904, P<0.001), tobacco use during/after therapy (RR=0.824, P<0.001), and 'bulky' tumors (RR=1.270, P<0.001) or large tumors (RR=1.332, P<0.001). In most previous studies, sex, age, comorbidities, tobacco use during/after RT, alcohol consumption, hemoglobin level, tumor stage, ACI, tumor size/volume, subglottic extension and grade, among others, were predictive factors for the survival of patients with early glottic squamous cell carcinomas following definitive RT. By contrast, in the present study, none of these clinical factors were indicative of RT failure in early-stage glottic carcinoma.

To the best of our knowledge, only a few studies have evaluated the dosimetric risk factors for local failure. Several studies investigated the association between total dose and local failure in early glottic carcinomas (18,20-26). The majority of those studies compared the total dose between ≤66 and >66 Gy with regard to local failure, which was not significantly different. The present study was the first to investigate the dosimetric factors of local failure for early-stage glottic carcinoma that was definitively irradiated to a prescription dose of 66 Gy. Furthermore, in the present study, the HI for glottic larynx did not reach the required levels of significance to be considered as a confounding factor. However, the P-value was reasonably low, confirming its importance. This finding indicates that techniques using RT for uniform dose distribution to the target volume, such as intensity-modulated RT (IMRT), may improve the local control rate for early-stage glottic carcinoma treated with definitive RT. Only a limited number of studies have evaluated the treatment outcomes of IMRT for early-stage squamous cell carcinoma of the glottis (27,28). In these studies, the local control rate did not differ significantly between patients treated with IMRT and those treated with RT. However, the prescription dose for patients treated with IMRT was 63 Gy/28 fractions. Therefore, there is potential for improving the local control rate in patients treated with IMRT by setting the prescription dose to 66 Gy/33 fractions, and the minimum dose of the glottic larynx to ≥65 Gy.

The main limitation of the present study was the possible selection bias for the predictive factors owing to the retrospective nature of the study. Therefore, prospective studies are required in the future to confirm our findings.

In conclusion, the minimum dose to the glottic larynx was the only factor found to be significantly associated with the occurrence of local failure. Setting the minimum dose to the glottic larynx at ≥65 Gy may improve the local control rate for early-stage glottic carcinomas irradiated to a prescription dose of 66 Gy.

Table VI. Dosimetric risk factors for local failure in all cases.

No.	Dose to glottic larynx (Gy)				Dose to CTV (Gy)				Dose to PTV (Gy)				Local control	Local control duration (months)
	Max	Mean	Min	HI	Max	Mean	Min	HI	Max	Mean	Min	HI		
1	68.5	67.0	65.4	1.047	68.6	65.7	62.2	1.103	68.6	65.2	36.7	2.024	Control	65
2	66.9	66.1	65.3	1.025	67.0	65.4	63.2	1.060	67.2	65.1	25.0	1.111	Control	132
3	66.5	65.9	64.8	1.026	66.6	65.2	61.0	1.092	66.9	64.5	51.3	1.823	Control	21
4	67.7	65.5	63.8	1.061	67.8	64.6	59.4	1.141	67.9	64.0	41.1	2.716	Control	123
5	68.4	66.3	64.5	1.060	68.1	65.5	61.1	1.115	68.4	65.1	49.6	1.333	Failure	2
6	66.6	66.4	66.0	1.009	66.7	65.8	63.8	1.045	66.7	64.8	35.9	1.623	Control	82
7	67.9	66.6	65.0	1.045	68.1	64.7	60.2	1.131	68.4	64.1	38.0	1.379	Control	102
8	67.9	67.3	66.1	1.027	67.9	65.9	62.1	1.093	67.9	65.1	52.4	1.891	Control	4
9	66.6	66.3	65.6	1.015	66.8	65.7	63.9	1.045	66.9	65.1	47.8	1.761	Control	105
10	66.5	66.0	65.5	1.015	66.5	65.1	62.8	1.059	66.6	64.6	42.2	1.271	Control	76
11	67.0	66.6	66.0	1.015	67.3	66.1	64.1	1.050	67.6	65.6	26.0	1.414	Control	98
12	66.9	66.0	64.2	1.042	67.0	65.0	61.7	1.086	67.0	64.5	19.0	1.588	Failure	94
13	67.5	66.4	65.0	1.038	67.4	64.9	62.4	1.080	67.6	64.3	24.5	2.600	Control	44
14	66.8	66.2	63.3	1.055	67.2	65.9	53.5	1.256	67.5	64.4	28.5	3.553	Control	107
15	66.2	65.8	65.1	1.017	66.6	64.9	62.7	1.062	66.7	64.3	57.8	2.722	Control	14
16	68.2	67.8	66.3	1.029	68.4	66.6	62.4	1.096	68.7	65.8	55.7	2.411	Control	95
17	66.2	65.6	64.4	1.028	66.2	65.0	62.5	1.059	66.5	64.7	35.3	1.151	Failure	6
18	66.6	66.2	65.6	1.015	66.7	65.4	63.0	1.059	67.1	65.0	39.7	1.205	Control	100
19	67.6	66.5	64.6	1.046	67.7	64.8	60.8	1.113	67.7	64.3	59.3	1.918	Control	106
20	67.3	66.1	64.7	1.040	68.4	65.3	59.4	1.152	68.4	64.7	26.9	1.723	Control	105
21	67.1	66.3	65.2	1.029	67.3	65.5	63.0	1.068	67.5	65.5	42.6	1.138	Control	71
22	67.8	66.9	64.3	1.054	69.0	65.2	58.7	1.175	69.0	63.9	35.1	2.565	Control	102
23	68.3	67.4	66.0	1.035	68.7	65.7	60.5	1.136	68.8	64.9	47.6	1.615	Control	93
24	70.2	67.9	65.6	1.070	70.3	65.9	60.7	1.158	70.3	65.5	46.3	2.003	Control	42
25	66.5	66.3	66.0	1.008	66.7	65.6	63.3	1.054	67.0	65.1	53.0	1.408	Control	99
26	69.3	67.4	65.2	1.063	69.3	65.3	60.2	1.151	69.3	64.9	47.4	1.497	Control	99
27	69.1	66.9	65.0	1.063	70.8	65.7	60.5	1.170	70.8	65.4	52.8	1.336	Control	58
28	70.4	67.7	65.2	1.080	70.4	65.6	54.9	1.282	70.5	65.0	28.9	1.487	Control	92
29	71.1	68.0	65.3	1.089	71.1	66.3	62.4	1.139	71.1	66.2	8.9	1.347	Failure	24
30	70.3	67.0	65.0	1.082	71.8	65.8	60.0	1.197	71.8	65.5	46.1	2.484	Control	17
31	69.6	67.9	66.3	1.050	70.1	66.0	60.3	1.163	70.1	65.1	57.8	7.876	Control	74
32	67.8	67.0	65.7	1.032	68.0	65.8	62.1	1.095	68.0	65.3	44.9	1.475	Control	78
33	69.6	67.1	64.8	1.074	69.5	65.9	62.7	1.108	69.6	65.7	22.9	1.204	Failure	12

Table VI. Dosimetric risk factors for local failure in all cases.

	Dose to glottic larynx (Gy)				Dose to CTV (Gy)				Dose to PTV (Gy)					
No.	Max	Mean	Min	HI	Max	Mean	Min	HI	Max	Mean	Min	HI	Local control	Local control duration (months)
34	67.9	66.1	64.0	1.061	68.5	64.7	57.9	1.183	68.9	63.8	13.6	1.535	Control	55
35	70.3	68.5	65.4	1.075	70.8	66.9	62.2	1.138	70.8	65.9	45.8	3.092	Failure	9
36	67.7	66.9	64.2	1.055	67.7	65.7	59.4	1.140	67.7	64.1	12.6	4.978	Control	69
37	66.6	66.2	65.7	1.014	66.6	65.8	62.8	1.061	66.6	65.3	39.1	1.454	Control	12
38	68.7	68.0	66.3	1.036	69.2	67.3	63.4	1.091	69.5	66.4	8.9	5.516	Control	53
39	67.4	66.7	65.8	1.024	67.8	66.2	63.8	1.063	68.9	65.7	19.1	1.762	Control	52
40	68.5	68.1	66.5	1.030	69.0	67.0	60.6	1.139	69.2	65.2	34.5	7.775	Control	50
41	70.3	69.9	68.7	1.023	70.3	68.7	65.2	1.078	70.3	67.6	41.7	3.681	Control	57
42	69.0	67.8	66.2	1.042	69.6	67.1	63.3	1.100	69.6	66.2	23.7	2.017	Control	50
43	69.0	68.3	67.1	1.028	69.0	67.5	65.2	1.058	69.0	66.6	47.3	1.655	Control	48
44	70.3	68.9	67.2	1.046	70.3	67.5	62.1	1.132	70.3	66.6	45.9	2.966	Control	48
45	68.9	68.4	67.3	1.024	68.9	67.5	63.7	1.082	68.9	66.9	55.3	1.457	Control	48
46	68.2	66.9	66.0	1.033	68.7	66.0	59.1	1.162	68.7	65.2	25.8	1.497	Control	46
47	69.9	69.7	69.4	1.007	69.9	68.9	66.6	1.050	70.0	68.0	52.8	1.266	Control	47
48	67.7	67.5	66.7	1.015	68.6	66.7	63.9	1.074	68.8	65.8	31.9	2.667	Control	46
49	69.3	68.0	65.3	1.061	69.6	66.3	56.5	1.232	69.6	65.7	51.1	1.318	Control	40
50	69.5	68.6	66.9	1.039	69.5	67.3	62.3	1.116	69.5	66.8	37.7	2.179	Control	39
51	68.8	67.4	65.1	1.057	69.6	65.6	55.7	1.250	70.1	65.3	48.0	1.372	Control	24
52	69.2	68.2	66.5	1.041	69.2	66.3	61.1	1.133	69.2	66.0	59.8	1.836	Control	36
53	69.1	68.2	66.1	1.045	69.3	67.0	62.8	1.104	69.4	66.9	30.2	1.446	Control	35
54	70.3	69.3	66.8	1.052	70.5	67.7	62.3	1.132	71.5	67.7	22.0	1.196	Control	35
55	68.3	67.6	66.0	1.035	68.3	66.6	64.3	1.062	68.3	66.3	60.5	2.262	Control	32
56	70.3	69.7	68.2	1.031	70.4	67.8	64.8	1.086	70.5	67.5	35.3	3.205	Control	6
57	70.9	69.5	67.0	1.058	70.9	67.6	62.6	1.133	71.2	67.9	37.2	1.177	Control	29
58	69.3	67.6	65.6	1.056	70.4	66.7	61.0	1.154	70.6	66.6	59.4	2.000	Control	29
59	69.0	66.7	63.7	1.083	70.3	65.8	57.8	1.216	70.6	65.5	49.2	1.898	Control	21
60	68.5	67.4	65.4	1.047	68.5	65.4	61.0	1.123	68.7	65.7	49.8	1.157	Control	15
61	68.9	66.8	63.5	1.085	69.3	65.0	56.2	1.233	70.0	64.8	45.2	1.423	Control	9
62	69.9	68.9	66.8	1.046	70.1	67.5	63.9	1.097	70.3	67.6	49.2	1.412	Control	16
63	67.3	64.9	62.7	1.073	69.8	65.4	52.1	1.340	70.1	64.7	36.7	1.551	Control	12
64	69.9	67.9	65.3	1.070	70.7	66.2	58.8	1.202	70.7	65.8	25.0	1.437	Control	12

CTV, clinical target volume; PTV, planning target volume; HI, homogeneity index.

Acknowledgements

The authors wish to thank the radiographer Mr Hideaki Tiba, and Dr Yu Tajima, Department of Radiology, Tokyo Medical University Hospital, for their professional assistance.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

MO, TI, TS and ShS conceived the study, and wrote and revised the manuscript. RM, AS and SaS reviewed, collected and analyzed the data. JP, KT and KS designed the study and acquired the data. All authors contributed to the writing of the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of Tokyo Medical University Hachioji Medical Center (Tokyo, Japan) and patient written informed consent was waived due to the retrospective design.

Patient consent for publication

Patient consent for publication was waived due to retrospective design.

Competing interests

The authors declare that they have no competing interests.

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