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 prescription 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 schedule for T1 glottic carcinoma is 66 Gy/33 fractions. The local control rate for T1N0 glottic carcinoma treated with conventional fractionation schedule for T1 glottic carcinoma is 66 Gy/33 fractions. 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
The local control rate was plotted using the gross tumor volume and beam's eye view. The maximum, mean and minimum doses and the homogeneity index (HI) for the glottic larynx, CTV and PTV were calculated. The HI was calculated as the maximum dose divided by the minimum dose to the target volume. Three-dimensional RT was planned and 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 and beam's eye view are shown in Fig. 1. Irradiation was delivered via local portals (mostly 5x5x5-6 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.

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)   |
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.
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         | Yes              | 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                        |
local control rate for T1 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 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.
| No. | Max Dose to glottic larynx (Gy) | Mean | Min | Max Dose to PTV (Gy) | Mean | Min | Max Dose to CTV (Gy) | Mean | Min | Max | HI | Local control duration (months) |
|-----|-------------------------------|------|-----|---------------------|------|-----|---------------------|------|-----|-----|----|-------------------------------|
| 1   | 68.5                          | 67.0 | 65.4 | 1.047               | 68.6 | 65.7 | 62.2               | 1.103 | 68.2 | 65.2 | 36.7 | 2.024                         |
| 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                         |
| 3   | 66.5                          | 66.5 | 66.8 | 1.026               | 66.6 | 66.2 | 62.0               | 1.092 | 66.9 | 64.5 | 51.3 | 1.823                         |
| 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                         |
| 5   | 68.4                          | 66.3 | 64.5 | 1.060               | 68.1 | 65.5 | 61.1               | 1.115 | 68.4 | 64.5 | 49.6 | 1.333                         |
| 6   | 66.6                          | 66.4 | 66.0 | 1.090               | 66.7 | 65.8 | 63.8               | 1.045 | 66.4 | 64.1 | 35.9 | 1.623                         |
| 7   | 66.9                          | 66.6 | 66.0 | 1.045               | 66.9 | 67.3 | 62.0               | 1.103 | 66.9 | 64.1 | 38.0 | 1.379                         |
| 8   | 67.9                          | 67.0 | 66.1 | 1.027               | 67.1 | 66.9 | 62.1               | 1.093 | 67.9 | 65.1 | 32.4 | 1.891                         |
| 9   | 68.6                          | 67.3 | 66.1 | 1.015               | 68.6 | 66.8 | 62.9               | 1.045 | 68.6 | 66.3 | 47.8 | 1.761                         |
| 10  | 66.0                          | 66.0 | 66.0 | 1.015               | 66.1 | 65.7 | 62.0               | 1.045 | 66.1 | 64.9 | 37.8 | 1.217                         |
| 11  | 67.0                          | 67.0 | 66.0 | 1.015               | 67.1 | 66.1 | 62.0               | 1.045 | 67.1 | 64.9 | 37.8 | 1.217                         |
| 12  | 66.9                          | 66.6 | 66.0 | 1.042               | 67.0 | 66.4 | 62.0               | 1.090 | 67.0 | 64.4 | 42.2 | 1.214                         |
| 13  | 67.5                          | 67.0 | 66.1 | 1.038               | 67.4 | 66.4 | 62.4               | 1.086 | 67.5 | 64.5 | 26.0 | 1.414                         |
| 14  | 67.9                          | 67.2 | 67.0 | 1.055               | 67.2 | 66.9 | 63.5               | 1.076 | 67.5 | 65.1 | 24.5 | 1.487                         |
| 15  | 68.2                          | 68.0 | 66.8 | 1.068               | 68.1 | 66.6 | 62.7               | 1.096 | 68.2 | 65.5 | 26.0 | 1.414                         |
| 16  | 68.8                          | 68.0 | 67.0 | 1.067               | 68.1 | 66.6 | 62.7               | 1.096 | 68.2 | 65.5 | 26.0 | 1.414                         |
| 17  | 67.5                          | 66.8 | 66.0 | 1.029               | 67.3 | 66.4 | 62.9               | 1.046 | 67.3 | 65.5 | 35.3 | 2.115                         |
| 18  | 67.9                          | 67.0 | 66.1 | 1.029               | 67.3 | 66.4 | 62.9               | 1.046 | 67.3 | 65.5 | 35.3 | 2.115                         |
| 19  | 67.6                          | 67.0 | 66.1 | 1.046               | 67.1 | 66.4 | 62.4               | 1.090 | 67.1 | 65.5 | 26.0 | 1.414                         |
| 20  | 67.3                          | 66.5 | 66.0 | 1.045               | 67.1 | 66.4 | 62.4               | 1.090 | 67.1 | 65.5 | 26.0 | 1.414                         |
| 21  | 67.1                          | 66.4 | 66.0 | 1.025               | 67.0 | 66.4 | 62.3               | 1.080 | 67.0 | 65.5 | 26.0 | 1.414                         |
| 22  | 67.8                          | 67.0 | 66.0 | 1.058               | 67.4 | 66.4 | 62.7               | 1.090 | 67.4 | 65.5 | 26.0 | 1.414                         |
| 23  | 66.9                          | 66.4 | 66.0 | 1.035               | 66.5 | 66.4 | 62.4               | 1.080 | 66.5 | 65.5 | 26.0 | 1.414                         |
| 24  | 67.2                          | 66.9 | 66.0 | 1.070               | 67.3 | 66.4 | 62.4               | 1.090 | 67.3 | 65.5 | 26.0 | 1.414                         |
| 25  | 66.5                          | 66.4 | 66.0 | 1.035               | 66.5 | 66.4 | 62.4               | 1.090 | 66.5 | 65.5 | 26.0 | 1.414                         |
| 26  | 66.9                          | 66.3 | 66.0 | 1.058               | 66.3 | 66.3 | 62.7               | 1.090 | 66.3 | 65.5 | 26.0 | 1.414                         |
| 27  | 67.1                          | 66.9 | 66.0 | 1.070               | 67.2 | 66.4 | 62.4               | 1.090 | 67.2 | 65.5 | 26.0 | 1.414                         |
| 28  | 70.4                          | 67.7 | 66.3 | 1.089               | 70.4 | 66.3 | 62.0               | 1.122 | 70.5 | 65.5 | 28.9 | 1.289                         |
| 29  | 71.1                          | 68.0 | 66.3 | 1.089               | 71.1 | 66.3 | 62.4               | 1.122 | 71.1 | 65.5 | 28.9 | 1.289                         |
| 30  | 70.3                          | 67.9 | 66.0 | 1.080               | 70.4 | 66.3 | 62.1               | 1.119 | 70.4 | 65.5 | 28.9 | 1.289                         |
| 31  | 69.6                          | 67.9 | 66.3 | 1.105               | 69.6 | 67.9 | 62.1               | 1.119 | 69.6 | 65.5 | 28.9 | 1.289                         |
| 32  | 67.8                          | 67.0 | 66.7 | 1.032               | 68.0 | 66.8 | 62.1               | 1.105 | 68.0 | 65.5 | 28.9 | 1.289                         |
| 33  | 69.6                          | 67.1 | 66.8 | 1.074               | 69.5 | 67.5 | 62.7               | 1.105 | 69.6 | 65.5 | 28.9 | 1.289                         |
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 | Max | Mean | Min | HI | Max | Mean | Min | HI |
| 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 | 65.2 | 66.7 | 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 | 65.8 | 61.2 | 1.024 | 67.8 | 66.2 | 63.8 | 1.063 | 68.9 | 65.7 | 19.1 | 1.762 | Control | 52 |
| 40  | 68.5 | 66.5 | 60.6 | 1.139 | 69.0 | 67.0 | 60.6 | 1.078 | 70.3 | 67.6 | 41.7 | 3.681 | Control | 57 |
| 41  | 70.3 | 68.7 | 65.4 | 1.075 | 70.8 | 66.9 | 62.2 | 1.138 | 70.8 | 65.9 | 45.8 | 3.092 | Failure | 9 |
| 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 | 1.555 | 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 | 66.5 | 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 | 67.7 | 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.
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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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