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Radiotherapy for Glottic T1N0 Carcinoma with Slight Hypofractionation and Standard Overall Treatment Time: Importance of Overall Treatment Time

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Objective: We retrospectively investigated treatment outcomes in patients with glottic T1 carcinoma treated with 65 Gy in 26 fractions four times a week and discuss the importance of the overall treatment time.
Methods: Two hundred one patients with glottic T1 carcinoma were evaluated. Sixty-five Gray in 26 fractions were delivered for 200 patients, whereas 1 patient received 62.5 Gy in 25 fractions. We delivered radiotherapy once daily four times a week in this period, for a weekly dose of 10 Gy. Weekdays except Wednesday were treatment days.
Results: The overall survival rate was 96.8 $\pm$ 1.3% (standard error) at 3 years and 90.8 $\pm$ 2.2% at 5 years. The local control rate was 91.9 $\pm$ 2.0% at 3 years and 89.8 $\pm$ 2.3% at 5 years. In patients with an overall treatment time equal to or longer than 47 days, the local control rate was 82.6 $\pm$ 6.0% at both 3 and 5 years. In the patients with overall treatment time equal to or less than 46 days, the local control rate was 94.6 $\pm$ 1.9% at 3 years and 91.8 $\pm$ 2.4% at 5 years. There was a significant difference between these two groups ($P = 0.0349$). A severe late radiation reaction occurred in one patient. He experienced severe laryngeal edema that required tracheotomy at 6 months after the completion of radiotherapy. The tracheotomy was closed at 14 months after completion of radiotherapy.
Conclusions: Overall treatment time seems to be an important factor for a good local control rate for glottic T1N0 carcinoma even when treated with slight hypofractionation.

Key words: laryngeal cancer – T1N0 glottic carcinoma – radiation therapy – overall treatment time – dose per fraction

INTRODUCTION

Radiotherapy for glottic T1 carcinoma shows excellent clinical outcome. Several authors have reported an 80–90% local control rate (LC) with standard radiotherapy using a dose per fraction of 1.8–2.0 Gy and total dose of 66–70 Gy (1–5). Reddy et al. (2) reported a 5-year LC of 86.1%, with a dose per fraction ranging from 1.8 to 2.0 Gy and total dose ranging from 66 to 70 Gy (median 66 Gy). Medini et al. (3) reported a 3-year LC of 91.8% using a median dose fractionation of 1.75 Gy and median total dose of 70 Gy. Fein et al. (4) reported a 2-year LC of 89% using a median dose per fraction of 2 Gy and median total dose of 66 Gy. Nishimura et al. (5) reported a 5-year LC of 85% using a dose of 2 Gy per fraction and a total dose ranging from 60 to 66 Gy.

Some investigators have shown that the choice of dose per fraction is important for a good LC. Reddy et al. (2) reported that patients treated with dose fractions of 2 Gy showed a 90.2% LC, but patients treated with dose fractions of 1.8 Gy showed a 76.4% LC. Franchin et al. (6) reported that a dose per fraction of $<$225 cGy was associated with a poor LC. Yu et al. (7) reported that the 5-year LC was 84% for patients treated with dose fractions above 2 Gy, and 65.6% for patients treated with dose fractions of 2 Gy. Yamazaki et al. (8) reported the results of a randomized trial comparing a standard radiotherapy of 66 Gy in 33 fractions for a dose

per fraction of 2 Gy, and a new treatment schedule of 56.25 Gy in 25 fractions or 63 Gy in 28 fractions for a dose per fraction of 2.25 Gy. They reported that the 5-year LC was 77% for the standard radiotherapy and 92% for 56.25 Gy in 25 fractions or 63 Gy in 28 fractions. Gowda et al. (9) reported a 5-year LC of 93% following treatment with 50–52.5 Gy in 16 fractions and an overall treatment time (OTT) of 21–26 days. However, it may be difficult to distinguish between the effect of dose per fraction and the effect of OTT on the treatment outcome because a high dose per fraction is usually associated with a short OTT.

OTT is also important for a good LC. Reddy et al. (2) reported that patients treated with an OTT of <50 days showed a 92.6% LC, whereas patients treated for more than 50 days showed a 75.6% LC. Fein et al. (4) similarly reported that patients treated for <50 days showed good results. In a study using a logistic regression model, Nishimura et al. (5) reported that prolongation of the OTT for 1 week may cause a decline in the LC from 89 to 74% for glottic T1 carcinoma. Thariat et al. (10) reported that an OTT ≤ 45 days was associated with good results. In their study, the median total dose was 65 Gy in 44 days. Skladowski et al. (11) analyzed the data of 235 patients with glottic T1 carcinoma who had been treated with a dose per fraction ranging from 1.5 to 3.0 Gy, a total dose ranging from 51 to 70 Gy, and an OTT ranging from 24 to 79 days. They reported that a 1-day prolongation of OTT corresponded to a loss of 0.35 Gy.

There has been at least one report of radiotherapy using a large dose per fraction and relatively longer OTT for the treatment of glottis carcinoma. Randall et al. (12) reported the treatment outcome for 79 patients with glottic T1 carcinoma who received radiotherapy three times per week with a dose per fraction of 333 cGy, and a total dose of 60 Gy in 6 weeks. This schedule did not shorten the OTT. They reported that the LC was 92%. Their results were thus slightly better than those of standard radiotherapy—that is, 66 Gy in 33 fractions within 6.6 weeks. On the basis of this report, the dose per fraction would seem to be more important than the OTT. However, as far as we know, there has been no other report that used a large dose per fraction without a short OTT.

At our institute, our treatment for glottic T1 carcinoma was four times a week with a dose of 2.5 Gy per fraction, for a total dose of 65 Gy. This schedule had a treatment gap within the radiotherapy course and did not shorten the OTT, so that our results might show the effect of dose per fraction clearly. In this article, we retrospectively investigated the treatment outcome of our patients with glottic T1 carcinoma, who were treated with 65 Gy in 26 fractions four times a week, and discuss the importance of OTT and the dose per fraction.

PATIENTS AND METHODS

Patients

This retrospective study was approved by the Institutional Review Board. From April 1989 to September 2006, 205 patients with glottic T1 carcinoma (UICC) presented at our institution and received radical radiotherapy as an initial treatment. Four of these cases were considered inappropriate for evaluation of the late radiation reaction and were excluded: one of these patients had concurrent oropharyngeal carcinoma and was treated for both cancers simultaneously; one patient received elective nodal irradiation and two patients received concurrent chemotherapy using CBDCA. Thus, a total of 201 patients with glottic T1 carcinoma were evaluated.

One hundred eighty-three patients were male and 18 patients were female. The ages ranged from 33 to 94 years, with a median age of 65 years. All patients were staged by radiation oncologists and otolaryngologists at conference. Laryngoscopy was performed for all patients at the conference and the staging was discussed between radiation oncologists and otolaryngologists. One patient had Tis disease, 146 patients had T1a disease and 54 patients had T1b disease. No patients had lymph node metastasis. All patients had squamous cell carcinoma that was proved by biopsy.

Radiotherapy

All patients were treated with megavoltage equipment. One hundred twenty-nine patients were treated with Cobalt, 72 patients were treated with 4 MV photons and 3 patients were treated with 6 MV photons throughout. One patient was treated with 4 MV initially, and changed to 6 MV photons after 40 Gy. The standard choice of equipment at our institution changed over the study period; that is, Cobalt was used until November 1998, and Linac with 4 MV photons was used from August 1998. One of the three patients treated with 6 MV photons was treated in July 1997, but the other two were treated in August 2005 and 2006, respectively.

All patients were immobilized with a plastic mask. Computed tomography treatment planning was done for all patients. The radiation treatment planning system was an Xio system (CMS Co., Ltd, St Louis, MO, USA) for 11 patients, a Focus system (CMS Co., Ltd) for 80 patients, an Eclipse system (Varian Medical Systems, Inc., Palo Alto, CA, USA) for 4 patients and a Therac system (NEC Co., Ltd, Tokyo) for 106 patients.

All patients were treated with parallel-opposed lateral fields or, if the patient had a short neck, with anterior oblique fields with the gantry tilted up to 60° from the horizontal line. The angle was usually within 30°. Only three patients required a gantry angle of 60°.

A wedge was used for 200 patients. Only one patient was treated without a wedge. A physical wedge of 15° was used for 106 patients, a 30° physical wedge was used for 92 patients, a dynamic wedge of 15° was used for 1 patient and a 30° dynamic wedge was used for 1 patient.

Heterogeneity correction was used in 52 patients. The correction was performed using the Clarkson in Focus for 36 patients, using Batho Power Law in Eclipse for 4 patients, using the Convolution in XiO for 10 patients and using

superposition in XiO for 2 patients. Heterogeneity correction was not used in 149 patients. In our institute, when heterogeneity correction was used, the difference between Monitor Unit (MU) with heterogeneity correction and MU without heterogeneity correction was calculated. If the difference was larger than 5%, we discussed which MU should be used.

The field width (dorsoventral direction) ranged from 4 to 7.0 cm, with a median of 5.5 cm. The field height (craniocaudal direction) ranged from 4 to 6.5 cm, with a median of 5.0 cm. Sixty-five Gray in 26 fractions were delivered to the isocenter for 200 patients, with only 1 patient receiving 62.5 Gy in 25 fractions. We delivered radiotherapy once daily and four times a week during this period, for a weekly dose of 10 Gy. Weekdays except Wednesday were treatment days. When these days were public holidays, we treated patients on Wednesday in order to maintain four-times-per-week irradiation in principle. If the treatment was on schedule, the OTT ranged from 44 to 46 days. However, irradiation of four times per week was not maintained over the New Year holiday. The OTT ranged from 43 to 60 days, with a median of 45 days. A histogram of the OTT data is shown in Fig. 1. The third quartile of the OTT was 46 days. The number of patients with an OTT equal to or less than 46 days was 156, and the number of patients with an OTT equal to or greater than 47 days was 45. The reasons of prolongation of OTT are national holiday for 36 patients, mechanical trouble of Linac or cobalt for 3 patients, acute skin or laryngeal reaction for 2 patients, work-related matters for 2 patients and unknown from chart for 7 patients. Some patients had more than one reason.

Statistical Analysis

The follow-up period ranged from 45 days to 239.8 months for survival, and from 44 days to 239.8 months for local control. The median was 66.0 months for survival, and 66.0 months for local control, respectively. The patient characteristics are summarized in Table 1.

The overall survival rate (OAS), cause-specific survival rate (CSS) and LC were calculated using the Kaplan–Meier method. OAS, CSS and LC were measured from the first day of radiotherapy. Event for OAS calculation was any death. Death from causes other than glottic cancer was censored when calculating the CSS. Failure after radiotherapy was considered an event when calculating the LC. Surgical control after radiotherapy was not considered in this study. Statistical differences were calculated using a log rank test. All figures were expressed as the calculated value ± standard error (SE). SPSS software, version18.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

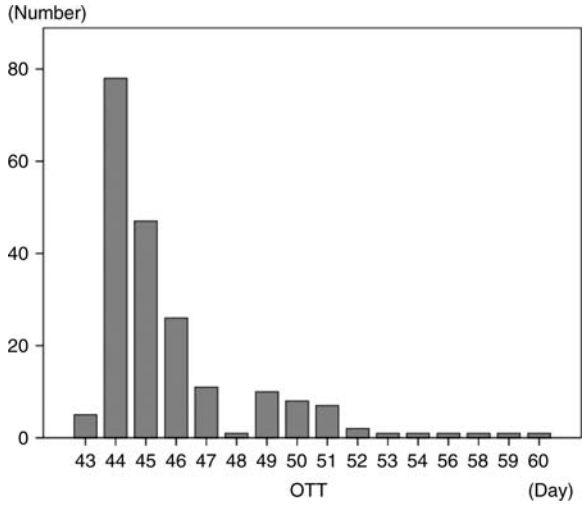

Figure 1. Histogram of the overall treatment time (OTT). The OTT ranged from 43 to 60 days, with a median of 45 days. The third quartile of OTT was 46 days.

Biologically Effective Dose Calculation

Using a linear-quadratic model, the biologically effective dose (BED) without a time factor was calculated as

$$\mathrm{BED}_{\alpha/\beta} = D(1 + d/(\alpha/\beta)).$$

The BED with a time factor was calculated as

$$\mathrm{BED}_{t\alpha/\beta} = D(1 + (\alpha/\beta)) - K(T - T_{\mathrm{delay}}),$$

Table 1. Patient characteristics

Age		33–94 y.o.	(median 65 y.o.)
Sex	Male	183	
	Female	18	
T stage	Tis	1	
	T1a	146	
	T1b	54	
Treatment energy	Co	126	
	4 MV photon	72	
	6 MV photon	3	
Field size	Craniocaudal direction	4.0–6.5 cm	(median 5.0 cm)
	Dorsoventral direction	4.0–7.0 cm	(median 5.5 cm)
Wedge	None	1	
	15°	106	
	30°	92	
	15° DW*	1	
	30° DW*	1	
Inhomogeneity	None	149	
Correction	Clarkson	36	
	Batho Power Law	4	
	Convolution	10	
	Superposition	2	

*DW, dynamic wedge.

where BED is the biologically effective dose delivered to the irradiated tissue, α/β is the inverse of the fractionation factor for the irradiated tissue, D is the total dose, d is the dose per fractionation, T is the OTT, K is the biological dose per day required to compensate for the loss of effect caused by the cellular population and T_{delay} is the lag time (from the initiation of treatment) before such fast repopulation begins. For head and neck tumors, the working values are $K = 0.9$ Gy day^{-1} and $T_{delay} = 28$ days, both of which have quite wide confidence intervals (13).

Other reports showing LCs of ~90% were reviewed and their BED_{10} and BED_{t10} values were calculated. When available, the median or mean of OTT was used to calculate BED_{t10}. In studies that did not report OTT clearly, we estimated OTT under the assumption that there was no treatment gap.

RESULTS

OAS, CSS and LC

The OAS was 96.8 ± 1.3% (SE) at 3 years and 90.8 ± 2.1% (SE) at 5 years. There was no death caused by glottic carcinoma. Figure 2 shows the Kaplan–Meier curve of OAS.

Twenty patients had recurrence. All of these patients had laryngeal recurrence. The LC was 91.9 ± 2.0% (SE) at 3 years and 89.8 ± 2.3% (SE) at 5 years (Fig. 3). There was no significant difference in the LC between T1a and T1b ($P = 0.358$), male and female gender ($P = 0.515$) or type of equipment used (Cobalt vs. Linac, $P = 0.229$). It takes 44–46 days to deliver 65 Gy in 26 fractions at four times per week without a treatment prolongation. Because 46 days is the longest OTT when treatment is delivered without treatment break period, we divided patients into two groups by OTT of 46 days. In the patients with OTT equal to or longer than 47 days, the LC was 82.6 ± 6.0% (SE) at both 3 and 5 years. In the patients with OTT equal to or less than 46 days, the LC was 94.6 ± 1.95 (SE) at 3 years and 91.8 ± 2.4% (SE) at 5 years. The difference in LC between these two groups was statistically significant (Fig. 4, $P = 0.0349$). Because only OTT is the significant factor for the LC, multivariate analysis was not performed.

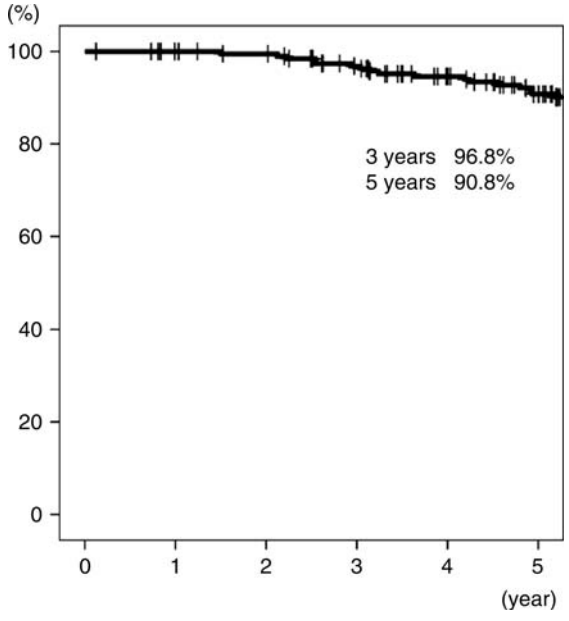

Figure 2. The overall survival rate (OAS) curve. The OAS was 96.8% at 3 years and 90.8% at 5 years.

Late Radiation Reaction

A severe late radiation reaction occurred in one patient. He experienced severe laryngeal edema that required tracheotomy at 6 months after completion of radiotherapy. The

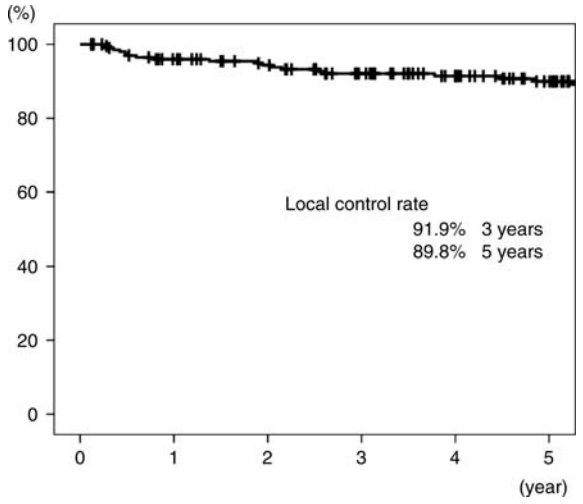

Figure 3. The local control curve for all patients. The local control rate was 91.9% at 3 years and 89.8% at 5 years.

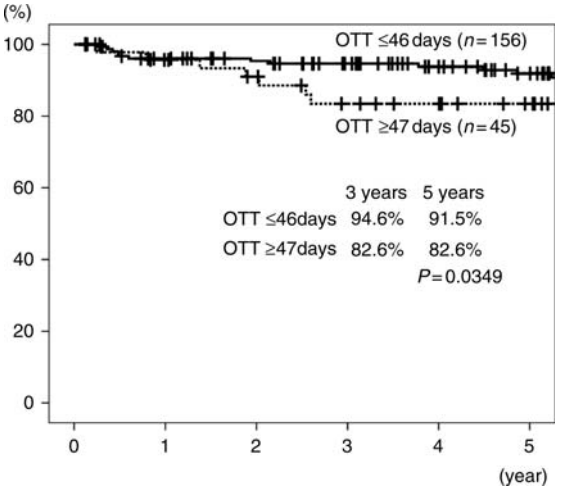

Figure 4. The local control curve for patients with an OTT ≤46 days and patients with an OTT ≥47 days. There was a significant difference in local control between these two groups ($P = 0.0349$).

Table 2. Other studies of radiotherapy for T1N0 glottic cancer

Author	Total dose (Gy)	Number of fractionation	OTT (day)	BED_{10} (GY_{10})	BED_{10} (GY_{10})	Local control (%)
Fein et al. (4)	66	33	49	79.2	60.3	89
Spector et al. (14)	66.5	33	45	79.9	64.6	89
Reddy et al. (2)	66	33	45	79.2	63.9	86.1
Medini et al. (3)	70	39	56	82.6	57.4	92.3
van der Voet et al. (15)	60	25	35	74.4	68.1	91
Gowda et al. (9)	50	16	21	65.6	65.6	93
Yamazaki et al. (8)	56.25	25	35	68.9	62.6	92

OTT, overall treatment time; BED, biologically effective dose.

tracheotomy was closed at 14 months after completion of radiotherapy. There was no recurrence at 148 months. There were no other severe late radiation reactions requiring surgical treatment.

Biologically Effective Dose

BED_{t10} ranged from 52.45 to 67.75 Gy_{10} in our study, and an OTT $\leq$46 days corresponds to a BED_{t10} larger than 65.05 Gy_{10}. BED_3 was 119.16Gy_3.

The BED_{10} and OTT values of reports that show LCs of ~90%, including the present study, are shown in Table 2 (2–4,8,9,14,15).

DISCUSSION

In this study, the LC for T1 glottic carcinoma was 91.9% at 3 years and 89.8% at 5 years. Severe laryngeal edema requiring tracheotomy occurred in only one patient (0.5%) whose tracheotomy was closed after 2 years, and there was no patient who needed a laryngectomy. We used four times per week irradiation with a dose per fraction of 2.5 Gy, and a total dose of 65 Gy. Using this schedule, the weekly dose was 10 Gy in our study, which was equivalent to standard radiotherapy using a dose of 2 Gy per fraction and five times per week irradiation. In the patients with OTT equal to or longer than 47 days, the LC was 82.6 $\pm$ 6.0% (SE) at both 3 and 5 years. In the patients with OTT equal to or less than 46 days, the LC was 94.6 $\pm$ 1.95 (SE) at 3 years and 91.8 $\pm$ 2.4% (SE) at 5 years. The difference in the LC between these two groups was statistically significant. OTT is therefore an important factor for a good LC.

Some investigators have reported that a long OTT in cases of glottic T1–2 carcinoma has a negative impact on the treatment outcome. Skladowski et al. (11) reported that a 10-day prolongation of OTT, from 45 to 55 days, decreased the tumor control probability by 13%. Nishimura et al. (5) reported that an OTT longer than 49 days was significantly associated with a poor LC. They reported that an only 1-week interruption of radiotherapy significantly reduced the 5-year local control probability of T1 glottic tumors, from 89 to 74%. Fein et al. (4) reported that an OTT equal to or longer than 50 days was associated with a poor 2 year LC for T1 and T2 disease. Nishimura and Fein reported that the dose per fraction did not have a statistically significant effect on the LC. In the present study, there was a significant difference in the LC between patients with an OTT $\leq$46 days and those with an OTT $\geq$47 days. Specifically, we found that the LCs for patients with an OTT $\leq$46 days were 94.6% at 3 years and 91.8% at 5 years, whereas those in patients with an OTT $\geq$47 days were 82.6% at both 3 and 5 years. This result agrees with the previous studies described above, and supports the idea that OTT plays an important role in the clinical outcome of glottic cancer treatment. However, because this study is retrospective and exploratory, our result does not mean that 47 days is a threshold for a good LC.

The OTT of our treatment schedule was similar to standard radiotherapy of 66 Gy in 33 fractions within 6.5 weeks. The largest difference between our schedule and standard radiotherapy was the dose per fraction. Because our results were not clearly superior to standard radiotherapy, it seems that a large dose per fraction is not clearly associated with a good LC for glottic T1 carcinoma. However, this hypothesis should be answered by properly a designed randomized control trial.

There have been several reports in which a large dose per fraction and short OTT were shown to be beneficial for glottic T1 carcinoma. van der Voet et al. (15) reported the results of several radiotherapy schedules with high dose per fraction and short OTT. About 80% of patients were treated with a dose per fraction over 2 Gy and OTT of $<$39 days. They reported that local control decreased with increasing treatment time. They also reported that radiotherapy of total 60 Gy in 25 fractions for 79 patients with glottic T1 carcinoma resulted in a 91% LC over 5 years with a 3.1% incidence of severe edema and necrosis at 5 years, and this schedule was the optimal treatment schedule. Gowda et al. (9) reported the results of radiotherapy for glottic T1 carcinoma using 50.0–52.5 Gy in 16 fractions over 21 days. The

5-year LC was 93% and severe late radiation complications occurred in one patient. Yamazaki et al. (8) reported a randomized trial comparing the results of two doses, 2 Gy per fraction and 2.25 Gy per fraction. They reported an LC of 92% at 5 years with 2.25 Gy per fraction and a total dose of 56.25 Gy in 25 fractions or 63 Gy in 28 fractions, which was superior to the LC of 77% at 5 years by the standard radiotherapy. There was no treatment gap in these reports, so that the OTT was ~1–3 weeks shorter than standard radiotherapy. These studies used a high dose per fraction and short OTT, and hence it seems impossible to distinguish the effects of dose per fraction and OTT in these studies. Franchin et al. (16) reported that daily doses of 1.80, 2.00 and 2.25 Gy resulted in 5-year LCs of 80, 91 and 88%, respectively, and found that the fraction size was a significant factor on disease-free survival in their univariate analysis. However, their results may also have reflected the effects of the short OTT.

Although it is difficult to distinguish the effects of dose per fraction and OTT, it may be important to discuss these effects separately, because the escalation of dose per fraction and shortening of OTT may have different biological effects on tumor cells. Shortening of OTT is useful for overcoming tumor repopulation and achieving a good LC for tumors that have a high α/β ratio and short potential doubling time. A large dose per fraction is beneficial because of the short OTT, not because of any direct effects exerted by the large dose per fraction. However, tumors that have a low α/β ratio, such as prostate cancers, may benefit from the use of a large dose per fraction because of the direct effects of the fraction size (17,18). The effects of the dose per fraction and the OTT are sometimes confused. However, it is important to discuss their effects separately, because their biological bases are different.

Our results may show the importance of BED with a time factor (BED_t). The BED_{t10} values in our schedule ranged from 52.45 to 67.75 Gy_{10} with a median of 65.95Gy_{10}. The BED_{t10} of OTT within 46 days was equal to or larger than 65.05 Gy_{10}. Our treatment schedule shows slightly high BED_{t10} compared with standard 66 Gy in 33 fractions with BED_{t10} of 60.3 Gy_{10} (OTT = 49) (4). This may be the reason why our LC was comparable to that by standard radiotherapy. The BED_{t10} values of the short OTT schedule are shown in Table 2. It seems that a BED_{t10} of ~60Gy_{10} is needed for good local control. Medini et al. (3) reported achieving a good LC using a low dose per fraction. In their study, the 3-year LC was 91.8% with a median total dose of 70 Gy and median dose per fraction of 1.75 Gy. A larger total dose may be needed to overcome the negative impact of prolongation of OTT on the local control. This previous report suggests that BED with a time factor should be the most important factor for achieving a good LC. In the present study, a BED_{t10} of 65 Gy_{10} was needed for a good LC. However, because there are estimates for which the confidence interval is wide in this model, BED_{t10} should be considered only as a guide. At the present time, however, we have no better model to compare different fractionation radiotherapy schedules.

Hypofractionation has a negative impact on the late radiation reaction in general. Harrison et al. (19) reported that laryngectomy/tracheostomy-free survival was significantly worse in Tis/T1 patients receiving hypofractionated treatment (5.5–6.6 Gy per week, total dose of 12–46.2 Gy). Randall et al. (12) also reported that moderate-to-severe laryngeal edema occurred in 10% of patients who received 60 Gy in 18 fractions within 6 weeks (three times per week irradiation). In our present series, however, only one patient (0.5%) had laryngeal edema requiring tracheotomy. Our schedule thus seems to be safer than the previously reported hypofractionation schedules. The reason why our schedule was associated with a relatively mild late radiation reaction may have been the relatively lower dose per fraction compared with previous reports. The BED_3 of our study was ~119.2 Gy_3, vs. the BED_3 of ~126.6 Gy_3 in the study of Randall. This small difference might explain the difference in the late radiation reaction between the two studies. In addition, our study had a retrospective design, and thus it was difficult to obtain precise information about mild radiation damage. Because of this limitation of the present study, we cannot rule out that mild radiation damage may have occurred frequently in our schedule.

In conclusion, by using a dose of 65 Gy in 26 fractions within 6.5 weeks, we achieved an LC of 91.9% at 3 years and 89.8% at 5 years. Our results suggested that the dose per fraction was not clearly associated with a good control rate. However, in patients with an OTT $\leq$ 46 days, the LC was 94.6% at 3 years and 91.8% at 5 years. Thus, the OTT was an important factor in achieving good local control. Severe laryngeal edema requiring tracheotomy occurred in only one (0.5%) patient. The present analysis, as well as a review of the literature, suggests that a sufficient BED_t is needed to achieve good local control.

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Conflict of interest statement

None declared.

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