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A multicenter survey of stage T1 glottic cancer treated with radiotherapy delivered in 2.25-Gy fractions in clinical practice: An initial 5-year analysis

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ABSTRACT

The purpose of this study was to evaluate the acute and late toxicity as well as local control (LC) in T1 glottic cancer (GC) patients treated with hypofractionated radiotherapy (RT) in clinical practice. The Tokai Study Group for Therapeutic Radiology and Oncology started RT treatment with a dose of 2.25 Gy for T1 GC in 2011. Ten institutions combined data from 104 patients with T1 squamous cell carcinoma between 2011 and 2015. In total, 104 patients with T1 GC were irradiated with a standard radiation dose of 63 Gy in 28 fractions.The median follow-up duration was 18 (3.7–49.5) months. Acute grade 3 adverse events were observed in 7 patients, with 4 patients (5%) having dermatitis and 3 patients (4%) having mucositis. Late adverse events above grade 3 were not observed. Two patients developed local recurrence. The rates of acute adverse events in the present study were comparable to those in previous studies that have used 2 Gy fractions of RT.

Key Words: T1 glottic cancer, radiotherapy, fraction size, hypofractionation

INTRODUCTION

According to the recently published guidelines for the treatment of head and neck cancer[1,2] all patients with T1-T2 laryngeal cancer should be treated, at least initially, with the intent of larynx preservation. The recommended strategies for early glottic cancer (GC) with the intent of larynx preservation are radiotherapy (RT), transoral laser surgery, and partial laryngectomy. Therefore, early stage GC is a good candidate for definitive RT. The 5-year local control (LC)

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rates for T1 GC treated with RT have been reported in the range 73.6–94% in the T1 larynx.[3-12)]

At 10 institutions in the Tokai District, Japan,[8)] the 5-year LC rates for T1a and T1b GCs treated with RT alone between 2000 and 2005 were reported to be 86.5% and 83.6%, respectively. These results were not consistent with those reported by other institutions.[3, 7, 9-10)] The 5-year LC rates reported by other institutions were more than 90% for T1a and T1b tumors. Definitive RT for T1 GC using a dose of ≥2.25 Gy per fraction has been reported to yield a higher response rate compared to 2 Gy per fraction. In addition, because of the increase in the number of patients who require radiotherapy treatment, reducing the treatment duration helps avoid delays in the administration of starting RT in new patients.[13-14)]

We, the Tokai Study Group for Therapeutic Radiology and Oncology (TOSTRO), started definitive RT for T1 GC using a RT dose of 2.25 Gy per fraction in 2011. In our institute and others, we administered a hypofractionated RT dose of 2.25 Gy for T1 GC, and aimed for a better outcome without increasing adverse events in clinical practice.

In the present study, we reported the initial 5-year experience for the 10 institutes of TOSTRO.

PATIENTS AND METHODS

TOSTRO administered a questionnaire survey concerning the administration of RT for T1 GC. This questionnaire is summarized in Table 1. This study was approved by the institutional review board of the Nagoya University Hospital, and after approval of the ethics committee of each participating institution, anonymized treatment information was collected in the form of a questionnaire. A retrospective analysis was performed on 104 eligible patients.

Patients aged >20 years with T1 glottic squamous cell carcinoma who underwent RT alone were included in the analysis. Three-dimensional treatment planning was performed for all patients with patients placed in a supine position and immobilized with thermoplastic masks. A standard radiation dose of 63 Gy was administered in 28 fractions (2.25 Gy per fraction). The

Table 1 Questionnaire item

1	Age, sex, and PS
2	T-stage: T1a / T1b
3	Tumor type: Exophytic / Superficial / Ulcerative
4	Anterior commissure invasion; yes or no
5	Tumor size: Is larger than two thirds of the vocal cord?
6	Irradiation starting date, ending date, and break period
7	X-ray beam energy, dose fractionation, and total radiation dose
8	Primary response and local control
9	Regional lymph node metastases; yes or no, distant metastases; yes or no
10	Alive or dead, the date last verified
11	Acute adverse effects, late adverse effects (CTCAE ver. 4.0)
12	Secondary treatments
13	Secondary cancer

ECOG, Eastern Cooperative Oncology Group; CTCAE: Common Terminology Criteria for Adverse Events; PS, Performance status

patients were treated using lateral opposed fields, and weighted beams and wedges were used as appropriate to improve dose homogeneity (field size, approximately 5 × 5 cm).

In a periodic follow-up, symptoms occurring in the interval between the initiation of RT and 90 days after this time point were classified as acute adverse effects. Late adverse events were defined as those appearing 3 months after the completion of the treatment. The evaluation of acute adverse events and late adverse events was performed using the Common Terminology Criteria for Adverse Events version 4.0.[15)]

RESULTS

Data collected from 10 institutes of TOSTRO were analyzed. The results were summarized in Tables 2–5. In total, there were 98 men and 6 women subjects. The median age was 71 (44–88) years. Seventy-one patients were stage T1a (74%) and 28 patients (27%) had anterior commissure invasion. Sixty-two patients (60%) had exophytic and 35 patients (34%) had superficial tumor types. Sixty-three patients (61%) had localized lesions and 41 (39%) had extended lesions (≥2/3 in vocal cord length). The details of the analysis are demonstrated in Table 2.

Treatment factors and outcomes are summarized in Table 3. Sixty-seven patients (64%) were treated using a 4 MV treatment beam and 37 (36%) patients were treated using a 6 MV treatment beam. The total dose range was 56.25–67.5 Gy and 96 patients (92%) received an RT dose of 63.0 Gy. The median follow-up period was 18 (3.7–49.5) months. Complete local response was achieved in 102 patients (98%) and 2 patients showed local recurrence. Acute grade 3 adverse events were observed in 10 patients; 7 with dermatitis (7%) and 3 with mucositis (3%) (Table 4). For the assessment of late adverse events, we evaluated the 85 patients who were followed up for more than half a year (Table 5). There were no late adverse effects above grade 3 at the time. Nine patients (11%) had overall treatment times ≥44 days owing to periods of infectious diseases in 2 patients and long holidays in 7 patients. The details of the 2 patients who experienced local recurrence are summarized in Table 6.

Secondary cancers were observed in 11 patients (11%) and no evidence of regional lymph node metastases and/or distant metastases were observed during the follow-up period.

Table 2 Patient characteristics

Characteristics	No. of Patients (%)
Sex	
Men	98 (94)
Female	6 (6)
Age	
Median	71 y.o
Range	44 – 88
Performance status	
0	68 (65)
1	30 (29)
2	6 (6)

Classification of tumor	
T-stage	
T1a	71 (74)
T1b	33 (26)
Anterior commissure invasion	
no	76(73)
yes	28 (27)
Tumor type	
Exophytic	62 (60)
Superficial	35 (34)
Ulcerative	7 (6)
Tumor size	
localized (<2/3 of vocal cord)	63 (61)
extended (≥2/3 of vocal cord)	41 (39)

Table 3 Treatment factors and possible outcomes

Treatment factors	No. of Patients (%)
Energy	
4 MV	67 (64)
6 MV	37 (36)
Dose (Gy)	
56.25	5 (5)
60.75	1 (1)
63.00	96 (92)
67.50	1 (2)
Treatment outcome	
Response	
CR	102 (98)
PR	1 (1)
NC	0 (0)
Unknown	1 (1)
Local failure	
Yes	2 (2)
No	101 (97)
Unknown	1 (1)
Overall treatment time (days)	
Median	41
Range	33–50

Follow-up (months)		
	Median	18
	Range	3.7– 49.5
Status		
	Alive	99 (95)
	Dead	5 (5)
Secondary cancer		
	Yes	11 (11)
	No	92 (88)
	Unknown	1 (1)

CR, Complete response; PR, Partial response; NC, No change

Table 4 List of acute adverse events categorized according to the Common Terminology Criteria for Adverse Events ver. 4.0

Acute adverse events (n = 104)	G0 (%)	G1 (%)	G2 (%)	G3 (%)	G4 (%)
Dermatitis	0	73 (70)	24 (23)	7 (7)	0
Laryngeal mucositis	1 (1)	66 (63)	34 (33)	3 (3)	0
Laryngeal edema	48 (46)	53 (51)	3 (3)	0	0
Laryngeal hemorrhage	100 (96)	4 (4)	0	0	0
Pharyngolaryngeal pain	9 (9)	66 (63)	29 (28)	0	0

Table 5 Common Terminology Criteria for Adverse Events ver. 4.0

Late adverse effects (n = 85)	G0 (%)	G1 (%)	G2 (%)	G3 (%)	G4 (%)
Hoarseness	65 (63)	19 (29)	1 (2)	0	0
Laryngeal necrosis	85 (100)	0	0	0	0
Laryngeal edema	68 (80)	17 (20)	0	0	0
Laryngeal hemorrhage	85 (100)	0	0	0	0
Pharyngolaryngeal pain	75 (88)	8 (9)	2 (3)	0	0

Table 6 Local recurrences

No.	Gender/Age	PS	T	Tumor type	Energy	Dose (Gy)	OTT (days)	Time of LF (Mo)	ST	Status
1	Male / 88	0	T1b	Exophytic AC (+) extended	4 MV	63.0	43	4	No	Alive with cancer at 8 months
2	Male / 70	2	T1a	Superficial	6 MV	56.25	44	16	No	Dead with HF in 20 Mo

PS, performance status; OTT, overall treatment time; AC, anterior commissure invasion; LF, local failure; Mo, months; LF, local failure; Mo, months; ST, salvage treatment, HF, heart failure

DISCUSSION

Laryngeal cancer is the most common cancer among the head and neck cancers. RT is an effective treatment method for early GC with the advantage of larynx preservation. The 5-year LC rates of stage T1 GCs treated with RT were approximately in the range 73.6–94%.[3-12] The 5-year LC rates for stages T1a and T1b GCs treated with RT alone were previously reported by the 10 institutes in the TOSTRO group to be 86.5% and 83.8%, respectively.[8] A LC rate above 90% could not be achieved. In the retrospective analysis, definitive RT for stage T1 GC administered in ≥2.25 Gy fractions was previously reported to yield a higher response rate than that administered in 2 Gy fractions.[3, 10] Moreover, recent randomized studies have shown an improvement in the LC rates of patients with stage T1 or T1a GC when the total planned radiation was delivered over a shorter overall treatment time using high-dose fractionation.[9, 11] In addition, no significant differences were observed in the incidences of acute or late skin toxicities, mucous membrane, or larynx between the two treatment arms.

In the present study, we analyzed the accumulation results of the fractions that were modified from 2.0 Gy to 2.25 Gy in dose. 2 out of 104 patients showed recurrence. The details are summarized in Table 6. One of the patients was an elderly patient with a bulky stage T1 tumor that involved the anterior and posterior commissure. The primary effect was a partial response and the tumor was residual, but salvage operation could not be performed due to a very old man. The patient was still alive with cancer at the time of the study.

According to the report[12] that evaluated 208 stage T1 GC patients in a retrospective analysis, both the tumor bulk and anterior commissure involvement were significant factors for the LC rate in univariate analysis and tumor bulk was identified as the only significant factor for the LC rate in multivariate analysis. Although the benefits of hypofractionation have already been reported in a single-institution randomized trial for stage T1 GCs by Yamazaki *et al.*,[9] the multi-institutional randomized study conducted in Korea[11] could not statistically demonstrate the non-inferiority of the hypofractionation arm compared to the conventional fractionation arm. However, in a subgroup exploratory analysis of stage T1a disease, the 5-year local progression-free survival trended positively in the hypofractionation arm (76.7% vs. 93.0%; hazard ratio [HR], 3.65; p = 0.056). It was reported that they were unable to evaluate the effect of tumor bulk on the LC rate by hypofractionation.[11] We hypothesize that the LC rate of T1 with bulky or extended tumor is still inadequate, even if the dose has increased to 2.25 Gy.

The another local recurrent patient was superficial GC treated using a 6 MV treatment beam. His performance status was poor and he had many complications. The radiation dose administered was reduced to 56.25 Gy in 25 fractions. Nevertheless, the overall treatment time was prolonged. It was reported that the maintenance of the treatment was difficult. The treatment outcome in

early GC patients who received primary irradiation using a 6 MV treatment beam is limited and controversial.[3, 16-19] From fundamental research[20] with Monte Carlo simulation of radiation treatment for GC with 6 MV parallel-opposed photon beams in the CT-based model of the neck, the significant underdosage at the air-tissue interface in the larynx occurs in traditional RT treatments, especially in the glottic part of the larynx.

We hypothesized this case had local recurrence because of the prolongation of the overall treatment time, less total dose, and underdosage of the tumor.

The present study was at its 5th year of long-term follow-up at the time of the writing of the report and further long-term follow-up is required. If an increase in adverse events has not been observed and the improvement of LC compared to the 2 Gy has been likewise obtained, this treatment method is very useful and beneficial in clinical practice due to the reduction in the treatment period. Further investigation is recommended for its local control and the development of late adverse events.

In conclusion, the rates of acute adverse events in a multicenter survey for stage T1 GC patients treated with 2.25-Gy fractions were comparable to those in previous studies that used 2 Gy in fractions. The local control of GC appears to be good and we are gratified at the results. However, further investigation is required for its local control and late adverse events.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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