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Importance of total radiation dose and overall treatment time in T1 early glottic cancer

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► ***Original article***

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ABSTRACT

Background: In this study, we retrospectively reviewed the treatment outcome of 63 patients with T1 early glottic cancer treated with RT alone to determine the treatment outcome and the prognostic factors affecting local control. ***Materials and Methods***: All patients were treated by 6 MV photons with conventional bilateral fields up to a median dose of 66 Gy in 33 fractions. ***Results:*** The 5-year local control rate and overall survival were 77.7% and 93.1%, respectively. The total radiation dose with a cut-off value of 66 Gy was a significant prognostic factor for local control. The 5-year local control rate was 54.5% in patients treated with less than 66 Gy compared to 85.7% in patients treated with 66 Gy or higher dose (p = 0.014). In subgroup analysis, in patients who received 66 Gy or higher doses, all recurrences developed in whose overall treatment time was 49 days or longer, although the statistical significance was marginal (p = 0.066). ***Conclusion:*** This study showed that a total dose of 66 Gy or higher is required for the treatment of T1 glottic cancer, and delivering the total dose within 49 days seems important for local control.

Keywords: *Early glottic cancer, radiation therapy, radiation dose, treatment time.*

INTRODUCTION

Laryngeal cancer is the most common head and neck cancer excluding the skin with the age-standardized incidence rate of 1.4 in South Korea in 2012 [1]. Laryngeal cancer is usually diagnosed at an early stage because hoarseness is commonly present in the early time. Nearly 55% of laryngeal cancers are diagnosed at the T1N0 stage [2]. The treatment of choice in early glottic cancer is still controversial because no prospective randomized trials comparing radiation therapy (RT) and surgery exist [2]. Although some studies found that voice quality after RT was better than that after surgery, the level of evidence was low [2, 3]. Therefore, the treatment option is usually chosen based on local expertise or patient preference. The outcomes of RT alone have been reported by several institutions with 5-year local control rates ranging from 75% to 94% for T1 disease [4-7], and from 45% to 73% for T2 disease [5, 8-10].

In this study, we report our experience of T1 early glottic cancer treated with RT alone. The long-term clinical outcome and the risk factors for recurrence were evaluated.

MATERIALS AND METHODS

From 1989 to 2012, 75 patients with early glottic cancer were treated with definitive RT at Gyeongsang National University Hospital. For

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this study, we selected the patients who satisfied the following criteria: 1) histopathologically confirmed as having invasive squamous cell carcinoma of the glottis, 2) clinically staged as T1N0 according to the 7th edition of the American Joint Committee on Cancer (AJCC), 3) no previous history of radiation to the head and neck area, and 4) followed up for at least 6 months. The staging work-up included physical examination, direct laryngoscopy, and computed tomography (CT) of the neck. Of the 75 patients, eight patients were in the T2 stage, three patients were lost to follow-up, and one patient had a history of previous radiation. Therefore, 63 patients were included in the analyses and we retrospectively reviewed the medical records of these patients. This study was approved by the institutional review board (IRB) of the Gyeongsang National University Hospital on June, 2015 (IRB No. 2015-06-032).

For simulation, all patients were immobilized with a thermoplastic mask in the supine position. After 2006, 3D simulation was performed and CT images of the neck was acquired by a Light Speed CT scanner (General Electric, Milwaukess, WI) in 3 mm slice thickness. All patients were treated by a conventional linac machine (Varian IX and EX, Varian Medical Systems, Palo Alto, CA) with 6 MV photons via parallel-opposed bilateral fields. RT was delivered with curative intent once daily, 5 days per week. The RT field was designed with a 2-dimensional (2D) simulator before 2006. The typical field borders were 1) superior: mid-thyroid notch, 2) inferior: lower border of the cricoid cartilage, 3) posterior: 1 cm posterior to the thyroid cartilage or anterior border of the vertebral body; 4) anterior: 1-1.5 cm anterior to the skin. After the introduction of a computed tomography (CT)-simulator in 2006, all patients underwent CT simulation and 3D planning. However, the RT field was identical with that of 2D simulation with field size ranging from 5 × 5 cm to 6.5 × 6 cm. Median radiation dose of 66 Gy (range: 60-70 Gy) was prescribed at the isocenter. The fraction size was 2 Gy except in 2 patients who were treated with 2.25 Gy per fraction, up to a total dose of 63 Gy.

All statistical analyses were performed with SPSS version 21.0 (Chicago, IL, USA). The overall survival and local control rate were defined as the time from the end of RT to any death or local recurrence, respectively, and they were calculated using the Kaplan-Meier method. The larynx preservation rate defined as the proportion of patients who did not undergo total laryngectomy, was also calculated using the Kaplan-Meier method. To identify prognostic factors independently associated with local control, the log-rank test and the Cox proportional hazards model were applied. Two-sided p values of < 0.05 were considered statistically significant. Since the doses per fraction varied, the total radiation dose was compared with the biologically effective dose (BED) in 2 Gy per fraction with a α/β ratio of 10 (EQD2) calculated as follows:

$$EQD2 = (\text{number of fractions}) \times (\text{dose per fraction}) \times (\alpha/\beta \text{ ratio} + \text{dose per fraction}) / (\alpha/\beta \text{ ratio} + 2)$$

In addition, to include the effect of overall treatment time, we also calculated the corrected BED (cBED) as suggested by Yamazaki *et al.*[11] for glottic cancer using the following equation:

$$cBED = EQD2 - 0.6 \times (\text{overall treatment time} - T_{lag}),$$

in which T_{lag} was assumed to be the lag period of 28 days for accelerated repopulation of the tumor cells.

The toxicities were assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Acute toxicity was defined when toxicity developed during or within 3 months after the treatment. Late toxicity was defined when toxicity developed 3 months after the end of RT.

RESULTS

Patient and treatment characteristics

Table 1 provides a summary of patient and treatment characteristics. All patients were

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males, and the median age was 61 years (range: 33-81 years). Both vocal cords were involved (T1b disease) in 10 (15.9%) patients, and the anterior commissure was involved in 14 (22.2%) patients. CT simulation and 3-dimensional (3D) planning were performed in 37 (58.7%) patients. The delivered RT dose in EQD2 was lower than 66 Gy in 18 (28.6%) patients and 66 Gy or higher in 45 (71.4%) patients. The median overall treatment time was 49 days (range: 40-90 days), and the median cBED was 55.2 Gy (range: 26.8-61.6 Gy).

Table 1. Patient and treatment characteristics (n=63)

Characteristics	N	(%)
Age, year	Median: 61	Range: 33-81
≤ 65	38	(60.3)
> 65	25	(39.7)
T stage		
T1a	53	(84.1)
T1b	10	(15.9)
Histology		
Well	36	(57.1)
Moderate	19	(30.2)
unavailable	8	(12.7)
AC involve		
No	49	(77.8)
Yes	14	(22.2)
RT planning		
2D	26	(41.3)
3D	37	(58.7)
Total RT dose / fraction (EQD2)		
63.0 Gy / 28fx (64.3 Gy)	2	(3.2)
60.0 Gy / 30fx (60.0 Gy)	6	(9.5)
64.0 Gy / 32fx (64.0 Gy)	10	(15.9)
66.0 Gy / 33fx (66.0 Gy)	19	(30.2)
70.0 Gy / 35fx (70.0 Gy)	26	(41.3)
Overall treatment time		
< 49 days	27	(42.9)
≥ 49 days	36	(57.1)
cBED		
< 55 Gy	27	(42.9)
≥ 55 Gy	36	(57.1)

Abbreviations: AC: anterior commissure; RT: radiation therapy; EQD2: Biologically effective dose in 2 Gy fraction with α/β ratio of 10; cBED: corrected biologically effective dose

Local control and survival

After a median follow-up of 50.5 months (range: 8.8 – 300.3 months), there were 14 local recurrences. Twelve recurrences developed within 2 years, and the other two recurrences developed at 42.4 and 70.1 months after the end of RT, respectively. The actuarial 3-, 5- and 10-year local control rates were 80.3%, 77.7%, and 73.2%, respectively (figure 1a). The 5-year local control rate for T1a and T1b tumors was 79.9% and 65.6%, respectively. All recurrences were identified within the glottis at the time of detection. Of the 14 recurred patients, 10 patients were salvaged with surgery (three patients with cordectomy, two patients with vertical hemilaryngectomy and five patients with total laryngectomy). The remaining four patients were transferred to another hospital and were lost to follow-up. The larynx preservation rate was 93.5% at 1 year after RT, and 91.5% after 2 years. The actuarial 3-, 5-, and 10-years overall survival were 96.3%, 93.1%, and 93.1%, respectively (figure 1b).

Prognostic factors affecting local control

Table 2 shows the results of univariate and multivariate analyses to identify the prognostic factors affecting local control rates. Only the total radiation dose calculated in EQD2 with a threshold of 66 Gy was a significant factor affecting local control. The 5-year local control rate was 54.5% in patients treated with less than 66 Gy compared to 85.7% in patients treated with 66 Gy or higher dose (p = 0.014) (figure 2). However, the local control rate did not differ between groups divided based on the overall treatment time (p = 0.465) or cBED (p = 0.626). Also in the multivariate analysis, the total radiation dose was the only significant prognostic factor affecting local control rates with a hazard ratio (HR) of 0.03 (p = 0.003, 95% confidence interval (CI): 0.01-0.32). The involvement of anterior commissure showed marginal significance with a HR of 5.00 (p= 0.053, 95% CI: 0.98-25.62).

In subgroup analysis, the overall treatment time was a significant factor for the group that received 66 Gy or higher doses. In this group, all six recurrences developed in patients whose overall treatment time was 49 days or longer. No recurrence developed in patients who received

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66 Gy or higher doses within 49 days. This showed a marginal significance in the Kaplan-Meier survival curve (p = 0.066) (figure 3a). However, the cBED showed no significance in the subgroup analysis.

Toxicity

The most common acute toxicities were dysphagia and skin reactions. Seven (11.1%) patients had grade 2 dysphagia and five (7.9%) patients had grade 2 radiation dermatitis. Of these patients, two patients suffered from grade 3 toxicity, one with dysphagia and the other with dermatitis. No grade 2 or higher late toxicities were recorded. Toxicity showed no difference according to the total radiation dose or overall treatment time (table 3).

Table 2. Univariate and multivariate analyses to identify factors associated with the local control rate

		Univariate		Multivariate		
Variable	No. (%)	5-year LC	p value	HR	p value	95% CI
Age, year			0.346		0.335	(0.11-2.16)
≤ 65	38 (60.3)	71.5		1		
> 65	25 (39.7)	87.2		0.48		
T stage			0.295		0.507	(0.06-4.05)
T1a	53 (84.1)	79.9		1		
T1b	10 (15.9)	65.6		0.49		
Histology			0.522		0.226	(0.59-9.50)
Well	36 (57.1)	79.2		1		
Moderate	19 (30.2)	70.7		1.86		
AC involve			0.112		**0.053**	**(0.98-25.62)**
No	49 (77.8)	82.2		1		
Yes	14 (22.2)	61.4		5.00		
RT planning			0.641		0.078	(0.83-39.97)
2D	26 (41.3)	76.9		1		
3D	37 (58.3)	76.5		5.74		
RT dose (EQD2)			0.014		**0.003**	**(0.01-0.32)**
< 66 Gy	18 (28.6)	54.5		1		
≥ 66 Gy	45 (71.4)	85.7		0.03		
OTT			0.465		0.085	(0.83-17.54)
< 49 days ≥ 49 days	27 (42.9) 36 (57.1)	79.6 76.5		1 3.82		
cBED			0.626			
< 55 Gy	27 (42.9)	77.8		N/A		
≥ 55 Gy	36 (57.1)	76.8				

Abbreviations: LC: local control rate; AC: anterior commissure; RT: radiation therapy; EQD2: Biologically equivalent dose in 2 Gy per fraction with α/β ratio of 10, OTT: overall treatment time; cBED: corrected biologically effective dose; HR: hazard ratio, CI: confidence interval; N/A: not assessed

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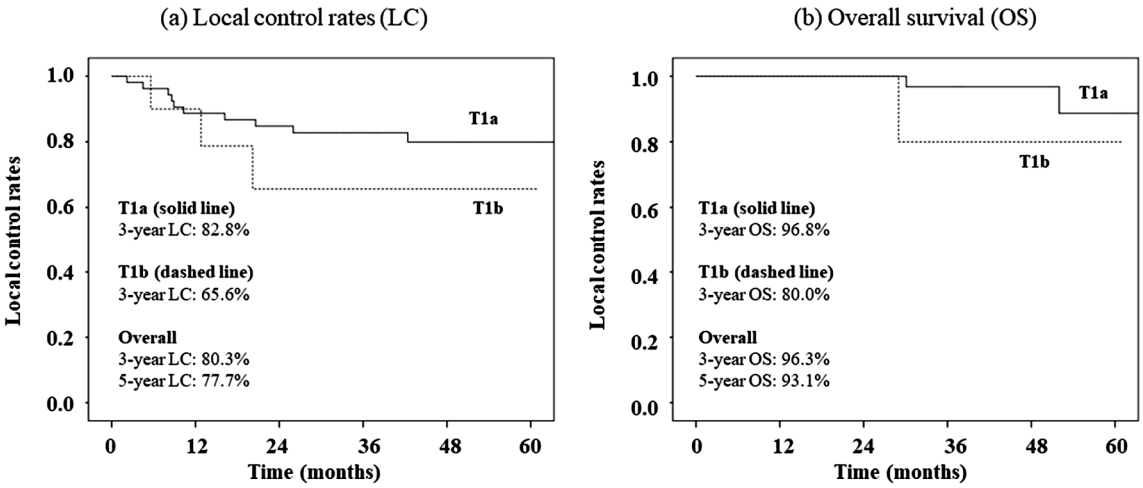

Figure 1. The clinical outcomes including (a) local control rates and (b) overall survival for early glottic cancer.

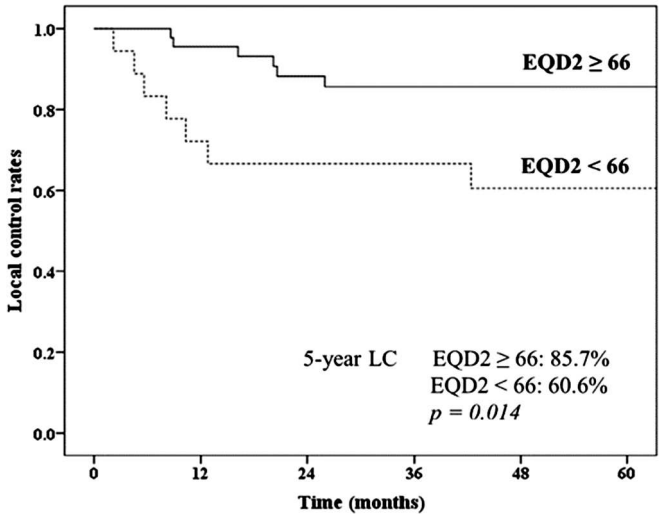

Figure 2. The local control rates between groups divided according to the total radiation dose shown in biologically equivalent dose in 2 Gy per fraction (EQD2) with a threshold of 66 Gy.

Table 3. Toxicity (Grade 2 or higher toxicities were recorded)

	No. of patients - Total (Grade 2 / Grade 3)	
	Dysphagia	**Dermatitis**
Total dose ≥ 66 Gy	5 (4 / 1)	4 (3 / 1)
Total dose < 66 Gy	2 (2 / 0)	1 (1 / 0)
OTT ≥ 49 days	3 (2 / 1)	2 (2 / 0)
OTT < 49 days	4 (4 / 0)	3 (2 / 1)
Overall	7 (6 / 1)	5 (4 / 1)

Abbreviations: OTT: overall treatment time

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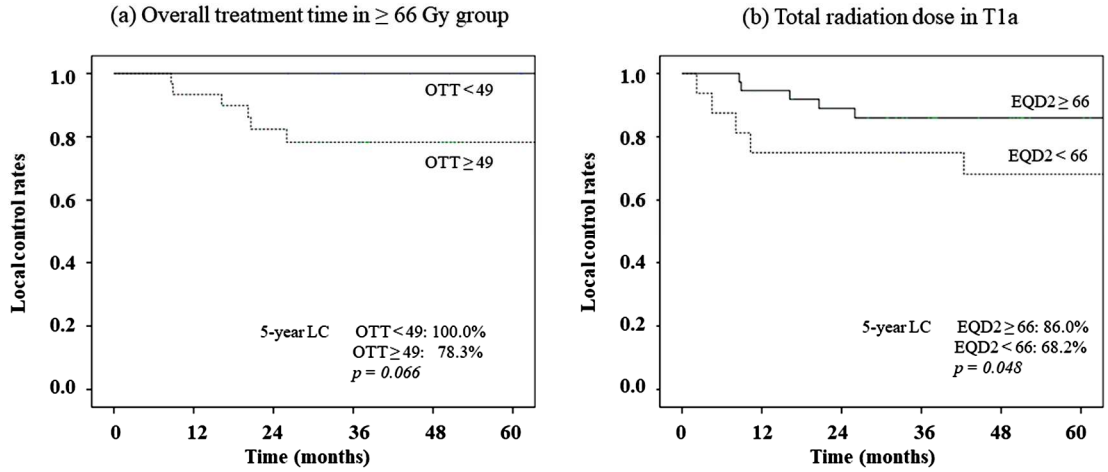

Figure 3. Subgroup analysis. (a) The difference in local control rates according to the overall treatment time in patients who received 66 Gy or higher dose (b) The difference in local control rates according to the total radiation dose in patients of the T1a subgroup.

DISCUSSION

Definitive RT is commonly used for the treatment of early glottic cancer since it provides treatment outcomes and voice-related quality of life comparable to transoral surgery [2]. If one decides to treat the patient with definitive RT, recent advances in the RT technique from conventional 2D to conformal 3D and IMRT make it difficult to choose a treatment modality. Several studies did not show a different local control or toxicity rate between 2D and 3D RT as our study.[9, 12, 13] IMRT can offer better conformity without compromising the target volume coverage and can decrease the dose to the carotid space as reported by several studies [14-16]. However, there is still no decisive clinical evidence that IMRT used for treatment of early glottic cancer can reduce the toxicity or enhance the treatment outcome. Some authors also suggest that there is a risk associated with IMRT because of the contouring error or under-dosing at the skin surface because of the limitations of dose calculation algorithms [14, 17]. Therefore, most of the patients are still commonly treated with the conventional 2D or 3D-based RT technique, and usually with bilateral fields as in our study.

To enhance the treatment outcome, we need to identify several prognostic factors affecting the local control rates, since local failure is the main type of failure in early glottic cancer. Various factors including higher T stage [5, 18], involvement of anterior commissure [6, 7, 18, 19], poor tumor differentiation [20, 21] and smoking [5, 22] have been reported as poor prognostic factors for T1 glottic cancer. In our study, only the total radiation dose was statistically significant in both univariate and multivariate analyses. The involvement of anterior commissure was marginally significant in multivariate analysis and the 5-year local control rate was quite different in the Kaplan-Meier analysis (82.2% vs. 61.4%, table 2).

Whether the adverse effect associated with the anterior commissure involvement is caused by anatomical properties or by the RT technique is still a source of controversy. Marshak *et al.* reported that the anterior commissure may represent a weak point for tumors, regardless of the RT technique [23]. This possibility is best explained by the Broyle ligament, which might be an anatomical cause of dehiscence of the perichondrium and might fail to prevent tumor invasion in patients with anterior commissure involvement. On the other hand, other investigators suggested that the anterior commissure can easily receive an underdose of radiation, depending on the type of energy used [24]. There is a greater risk of underdosage at the air-tissue interface with the depth-dose characteristics of 6 MV beams compared with those of cobalt-60. All patients in our study were

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treated with 6 MV beams, and this can be a factor for the low local control rate in patients with anterior commissure involvement. Tong *et al.* suggested that the negative impact of anterior commissure involvement can be overcome by using higher fraction size of > 2.0 Gy and a BED higher than 65 Gy with a α/β ratio of 15 [6].

The importance of radiation dose as a prognostic factor for local control has also been suggested by other investigators. Skladowski *et al.* and Sakata *et al.* suggested that higher doses with a threshold of 61 Gy or 50 Gy showed better local control rates for T1 glottic cancer [25, 26]. Nomiya *et al.* also reported that higher doses of 66 Gy are needed for T1b glottic cancer, although there was no significant benefit of total radiation dose above 64 Gy in T1a cancer [27]. In our study, higher dose with a threshold of 66 Gy was the most important prognostic factor for local control. In contrast with the result of the study by Nomiya *et al.* [27], 66 Gy or a higher dose was important in T1a disease in our study (figure 3b). The subgroup analysis result of T1b was limited because of the small number of patients.

In addition to total radiation dose, the time factor such as fraction size and overall treatment time is also a very important factor for head and neck cancers. Ferreira *et al.* concluded a strong significant relationship between time factor and local control exists based on the review of 62 head and neck cancer studies [28]. The importance of fraction size and overall treatment time has also been studied in early glottis cancer. Kim *et al.* and Ricciardelli *et al.* reported that 2.0 Gy per fraction significantly improved the local control compared to 1.8 Gy per fraction [13, 29]. The only prospective randomized study in early glottic cancer was performed by Yamazaki *et al.,* which compared 2.25 Gy per fraction and 2.0 Gy per fraction [11]. The total radiation dose was 60 Gy in 30 fractions or 56.25 Gy in 25 fractions for minimal tumors and 66 Gy in 33 fractions or 63 Gy in 28 fractions for larger tumors. The 2.25 Gy per fraction arm showed a superior 5-year local control rate (92% vs. 74%, p = 0.004), even though the BED was smaller. The authors recalculated the BED by incorporating the overall treatment time (named this the cBED) and concluded that this result is obtained due to the effect of shorter overall treatment time. In our study also, 2 patients were treated in 2.25 Gy per fraction up to a total dose of 63 Gy. However, both patients experienced local recurrence. The EQD2 was 64.8 Gy for these patients. Also, the cBED did not correlate with the local control rates. However, if the dose was 66 Gy or higher, then the overall treatment time was important. No recurrences were seen in patients who received 66 Gy or higher doses within 49 days, compared to six recurrences that developed in patients whose overall treatment time was longer than 49 days. This result was similar with that in the report by Nishimura *et al.*, which analyzed 120 T1-2 early glottic cancer patients [30]. They also concluded that the overall treatment time with a threshold of 49 days was important for local control, and they showed that 1-week interruption of RT reduced the 5-year local control rate from 89 to 74%.

It is difficult to draw a definite conclusion about the dose schedule from our study because of the limitations of this study. First, it was retrospective in nature, with relatively small numbers of cases. The small sample size might have limited our power to detect statistically significant differences. Second, although the field size and arrangement did not differ, patients treated by 2D simulation would might have some unacceptable dose distribution. This difference could have acted as a confounding factor.

However, notwithstanding these limitations, it seems clear that if one decides to treat T1 glottic cancer patients with conventional RT, a higher total dose above 66 Gy (EQD2) is needed, and delivering the total dose within 49 days seems important for local control. Prospective randomized studies are required to draw a firm conclusion about the correlations of total RT dose and overall treatment time.

***Conflicts of interest*:** *Declared none.*

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