Comparison of Three Fractionation Schedules in Radiotherapy for Early Glottic Squamous Cell Carcinoma

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Abstract. *Background/Aim:* Radiotherapy is widely accepted as the treatment of choice for early glottic squamous cell carcinoma (EGSCC), although it varies greatly with respect to dose, dose per fraction, and treatment techniques. The study aim was to evaluate the use of accelerated fractionation strategy (AFS) for EGSCC in standard clinical practice. *Patients and Methods:* Patients treated with definitive radiotherapy for EGSCC between 2008 and 2019 were retrospectively identified and received either conventional fractionation, hypofractionation, or hyperfractionation. *Results:* One hundred six patients were analyzed, and 19, 71, and 16 patients underwent conventional fractionation, hypofractionation, and hyperfractionation, respectively. The median follow-up was 56 months. The 5-year local control and overall survival rates were 79% and 83%; 78% and 79%; and 87% and 77%, respectively, and no significant difference was observed between the fractionation schedules. *Conclusion:* Our findings confirmed the utility of AFS in standard clinical practice and support its use for patients with EGSCC.

One duty of a multidisciplinary team is to evaluate and offer patients the best treatment options based on evidence of long-term functional outcomes after curatively intended therapy for

laryngeal cancer (1). Treatment options for T1-2N0 early glottic squamous cell carcinoma (EGSCC) include radiotherapy (RT), cordectomy, and laser microsurgery. Patients with EGSCC have shown excellent local control (LC) and survival rates, with voice quality preservation and low toxicity levels after undergoing RT (2); thus, RT is the preferred treatment option among these patients (3, 4). Although RT is widely accepted as the treatment of choice for early glottic cancer, it varies greatly with respect to dose, dose per fraction, and treatment techniques (5-9). The accelerated repopulation of surviving clonogenic tumor cells during the RT period, known to be a key factor determining the LC rate in head and neck cancer, has also been observed in patients with early glottic carcinomas. The LC rate of accelerated RT using an accelerated fractionation strategy (AFS) that reduces the overall treatment time (OTT) by either increasing the number of fractions per day (hyperfractionation) or increasing the dose per fraction (hypofractionation) has been reported to be superior to that of conventional fractionation (CF) with a 1.8-2.0 Gy daily schedule (10-13).

To our knowledge, there are no published studies that have compared the treatment results of CF, hypofractionation, and hyperfractionation as definitive RT for EGSCC. The purpose of this study was to evaluate the use of AFS for EGSCC in standard clinical practice.

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Key Words: Glottic cancer, radiation, hypofractionation, hyperfractionation, late-course accelerated hyperfractionation, altered fractionation.

Patients and Methods

Patients. We retrospectively reviewed the records of consecutive patients with T1-2N0M0 EGSCC who received definitive RT at our Institution between January 2008 and December 2019. With the aid of microlaryngoscopy, biopsy specimens were obtained from all patients, histopathologically examined, and proven to be squamous cell carcinoma. The stage of cancer was determined according to the seventh edition of the American Joint Committee on Cancer (14). This study was approved by the Institutional Review Board of the Kyoto Prefectural University of Medicine (approval number

ERB-C-1727). Written informed consent was obtained from each patient prior to treatment for publication of this article and any accompanying images.

Radiotherapy. The patients in a supine position were treated with fixation using thermoplastic masks. Three-dimensional conformal RT was administered by using two opposite parallel fields with or without a paired wedge and by modulating the field weight or performing dose normalization to improve the target coverage. Computed tomography-based radiation planning was performed with a slice thickness of 2 mm. RT was delivered by 4- or 6-MV linear accelerators. Gross tumor volumes were measured to include ≥ 2 -cm margins in all directions. Elective neck RT was not used for any of the patients. The minimum field size was 5×5 cm, centered over the mid-thyroid cartilage. The dose was prescribed at the intersection of beams in the mid-plane. Patients in the CF and hypofractionation groups received 60-70 Gy in 2.0-Gy daily fractions and 63-65.25 Gy in 2.25-Gy daily fractions, respectively, according to each patient's T stage. The patients in the hyperfractionation group received RT in the form of late-course acceleration to a total dose of 60 Gy in 45 fractions. In this group, RT was delivered to provide 30 Gy in 2.0-Gy daily fractions, and the remaining 30 Gy in 20 fractions was delivered as 1.5-Gy twice-daily fractions. Twice-daily treatments were delivered with a minimum inter-fraction interval of 6 hours.

Evaluation of treatment outcome and toxicity. The patients were regularly evaluated by performing laryngoscopy and physical examinations during the treatment period and at routine follow-up visits. During the treatment, patients were examined at least weekly. Once treatment ended, all patients were followed up every 1 to 2 months during the first 2 years and every 3 to 4 months thereafter. Acute and chronic treatment toxicities were documented according to the Common Terminology Criteria for Adverse Events version 4.0 (15). Follow-up data were obtained from the electronic medical records.

Statistical analysis. Overall survival (OS) was measured from the date of treatment initiation to the date of the last follow-up or death from any cause. Disease-free survival (DFS) was measured from treatment initiation to the first observation of any recurrence. LC was measured from treatment initiation to the first local recurrence. Laryngectomy-free survival was measured from treatment initiation to laryngectomy or death from any cause. OS, DFS, LC, and laryngectomy-free survival were calculated by using the Kaplan-Meier method. In the univariate analyses, differences between groups were estimated by performing the log-rank test.

All statistical analyses were performed in EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 2.13.0); EZR is a modified version of R commander (version 1.6-3) that was designed to add statistical functions frequently used in biostatistics (16). In all analyses, values of $p < 0.05$ were considered to indicate a statistically significant difference.

Results

Patient characteristics. One hundred and seven patients were enrolled during the study period; of these, one patient in the hypofractionation group was excluded because he refused

Figure 1. Patterns of fractionation over time. CF: Conventional fractionation; HYPO: hypofractionation; HYPER: hyperfractionation; RT: radiotherapy.

continuation of RT for personal reasons that were not related to treatment toxicity. Therefore, we evaluated 106 patients in total. There were 94 men and 12 women; the male-to-female ratio was 9:1. The median patient age was 70 years (range=47-88 years). Forty-eight (45%) and 58 (55%) patients had T1 and T2 tumors, respectively. Most patients had a good Eastern Cooperative Oncology Group performance status (0-1). There were 19, 71, and 16 patients in the CF, hypofractionation, and hyperfractionation groups, respectively. The median duration of treatment was 36 days (range=33-40 days) in the hyperfractionation arm, 41 days (range=38-55 days) in the hypofractionation arm, and 47 days (range=42-53 days) in the CF arm. All patients completed the planned RT schedule. Chemotherapy was concurrently administered with RT in 30 patients (28 in those with T2 tumors and two in those with T1 tumors). The most common regimen was weekly carboplatin, which was used in 23 out of 30 patients. The remaining seven received a triweekly regimen of cisplatin. Chemotherapy usage gradually decreased, and no patients have received it since 2016 (Figure 1). Analysis of fractionation with year as the period variable demonstrated significant declines from 2008-2011 to 2016-2019 in the use of both CF (from 34% to 4%) and hyperfractionation (from 37% to 0%), an overall period when hypofractionation was increasingly used (from 26% to 96%) (Figure 1). Table I summarizes the clinical characteristics of the 106 patients in the study population associated with the three fractionation schedules.

Follow-up and survival. The overall median follow-up duration was 56.3 months (range=3-130 months) from the initiation of RT. Among the 106 patients, five died of glottic

Table I. *Clinical characteristics.*

Characteristic	Group, n (%)		
	CF (n=19)	Hypofractionation (n=71)	Hyperfractionation (n=16)
Follow-up period, months			
Median (range)	60 (16-122)	41 (3-107)	101 (3-130)
Age, years			
Median (range)	71 (47-88)	70 (52-86)	64 (52-86)
Age, n (%)			
≤69 Years	8 (42%)	32 (45%)	12 (75%)
>69 Years	11 (58%)	39 (55%)	4 (25%)
Gender, n (%)			
Male	15 (79%)	65 (92%)	14 (88%)
Female	4 (21%)	6 (8%)	2 (12%)
PS, n (%)			
0	18 (95%)	67 (94%)	15 (97%)
1 or 2	1 (5%)	4 (6%)	1 (3%)
Hemoglobin, n (%)			
≤12.9 g/dl	7 (37%)	19 (27%)	7 (44%)
>12.9 g/dl	12 (63%)	52 (73%)	9 (56%)
T1	7 (37%)	35 (49%)	6 (38%)
T2	12 (63%)	36 (51%)	10 (62%)
CCRT, n (%)			
Yes	10 (53%)	10 (16%)	10 (62%)
No	9 (47%)	61 (84%)	6 (38%)

CCRT: Concurrent chemotherapy; PS: performance status; CF: conventional fractionation.

cancer and 14 died of other diseases, especially second primary cancer. The 2- and 5-year OS rates determined by the Kaplan-Meier method for all patients were 95.8% and 86.3%, respectively. Figure 2 shows a comparison of the OS rates between treatment groups. The 5-year OS rates in the CF, hypofractionation, and hyperfractionation groups were 83%, 79%, and 77%, respectively, and no significant difference was observed between treatment groups ($p=0.504$). Local recurrence was observed in a total of 18 patients, with four in the CF group, 12 in the hypofractionation group, and two in the hyperfractionation group. The median time to local recurrence was 8.6 months (range=3.6-36.2 months) after RT. Regional lymph node recurrence and distant metastases were observed in one and two patients, respectively. The 2- and 5-year DFS rates for all patients were 81.5% and 78.7%, respectively. After identification of local recurrences, 17 out of 18 patients underwent salvage surgery and one refused any salvage treatment. Eventually, seven patients underwent total laryngectomy. The 2- and 5-year LC rates for patients overall were 83.2%, and 80.4%, respectively. The 5-year LC rates in the CF, hypofractionation, and hyperfractionation groups were 79%, 78%, and 87%, respectively, and no significant

Figure 2. Overall survival curve by treatment group. No significant differences among the three fractionation schedules were observed. CF: Conventional fractionation; HYPO: hypofractionation; HYPER: hyperfractionation.

Figure 3. Local control curve by treatment group. No significant differences among the three fractionation schedules were observed. CF: Conventional fractionation; HYPO: hypofractionation; HYPER: hyperfractionation.

difference was observed between the treatment groups ($p=0.809$, Figure 3). For the entire group, the 5-year total laryngectomy-free survival rate was 70.4% (CF, 73.3%; hypofractionation, 67.2%; hyperfractionation, 66.3%; differences not significant). Table II presents the results of the univariate analysis for OS and LC. Age (≤69 vs. >69 years), clinical T stage (T1 vs. T2), hemoglobin level (≤12.9

Table II. Univariate analysis for overall survival (OS) and local control (LC) rates.

		n	5-Year OS (%)	p-Value	5-Year LC (%)	p-Value
Age	≤69 Years	52	87.8	0.084	80.3	0.905
	>69 Years	54	77.2		80.3	
Sex	Male	94	81	0.176	79	0.425
	Female	12	100		91.7	
PS	0	100	80.6	0.541	80.6	0.823
	1 or 2	6	75		75	
Hemoglobin	≤12.9 g/dl	33	81.2	0.835	75.6	0.436
	>12.9 g/dl	73	83.8		83.4	
Clinical T-stage	T1	48	86.2	0.309	82.6	0.439
	T2	58	79.7		79	
CCRT	Yes	30	88.7	0.535	81.8	0.849
	No	76	79.7		79.5	
RT	CF	19	83	0.504	78.9	0.809
	Hypofractionation	71	80.6		78.3	
	Hyperfractionation	16	86.7		86.7	

CCRT: Concurrent chemotherapy; OS: overall survival; LC: local control; PS: performance status; CF: conventional fractionation.

vs. >12.9 g/dl), and concurrent chemotherapy usage (yes vs. no) did not affect OS and LC.

Toxicities. Most of the patients, regardless of treatment group, had grade 1 or 2 mucositis and dermatitis during the treatment. One patient in the hypofractionation group developed grade 3 laryngeal edema, which responded to antibiotics and oral steroids. Treatment interruption was not experienced in this patient. Except for this case, no severe acute/chronic toxicities of grade 3 or higher were observed.

Discussion

In our study, the 5-year LC and OS rates were 80.4% and 86.3%, respectively, and we did not find significant differences among the three fractionation schedules. The rates of adverse events of grade 3 or greater in our study groups (<1% in all patients, 1.4% of hypofractionation) were comparable or slightly lower than the reported 1-3% range (3, 12, 17, 18). To the best of our knowledge, this is the first study that has directly compared the treatment results of CF, hypofractionation, and late-course accelerated hyperfractionation as definitive RT for EGSCC. The LC and OS rates in our study were comparable to those of recent prospective randomized studies involving hypofractionation (11, 13).

Prolongation of RT for head and neck cancer may worsen LC because of so-called ‘accelerated tumor clonogen repopulation during RT’, which leads to treatment resistance (19). Therefore, studies with intensification of AFS that reduces the OTT have been conducted either by increasing the dose per fraction (hypofractionation) or increasing the number of fractions per day (hyperfractionation). Some clinical results of definitive RT for EGSCC suggest that both

hypofractionation and hyperfractionation are beneficial for LC (6, 10). In a systematic review and meta-analysis of 1,762 patients, the benefit of accelerated fractionation RT persisted when each type of AFS was analyzed separately (6). This finding is in accordance with a single-institution retrospective analysis of 230 patients, which indicated that hyperfractionation schedules were similarly effective in terms of LC when compared with hypofractionation regimens with >2 Gy per fraction (20). These findings support the idea that either AFS (hypofractionation or hyperfractionation) may have a beneficial effect on LC. In our study, we used late-course accelerated fractionation in the hyperfractionation group. Despite being a variant of accelerated fractionation, late-course accelerated hyperfractionation is associated with minimal enhancement of acute reactions because it uses the concepts of accelerated fractionation while minimizing the volume of tissue irradiated with high doses. There are only limited data comparing late-course accelerated fractionation with other fractionation schedules of EGSCC (21). In our study, although many patients in the hyperfractionation group received chemotherapy, this fractionation schedule was found to be feasible and tolerable.

The Japanese prospective randomized trial by Yamazaki *et al.* that recruited 180 patients with only T1 tumors demonstrated significant LC gain with hypofractionation at 2.25 Gy per day compared with the CF (92% vs. 77%, $p=0.004$) (12). In contrast, a similar trial from Korea enrolling patients with T1 and T2 disease reported that use of the same dose per fraction led to non-significant improvement in local progression-free survival (11). A recent review by Sapienza *et al.* indicated that this LC benefit of AFS may not extend to T2 tumors because of the lack of a benefit in studies with predominantly T2 disease (6). In fact, a Radiation Therapy

Oncology Group trial (#9512) which recruited 239 patients with only T2 tumors failed to show a significant benefit of AFS (22), a finding that supported pooled study findings by Sapienza *et al*. In our study, more than half of the enrolled patients had T2 tumors, which may be one of the reasons why we did not find any benefits of AFS in LC.

At our Institution, the RT fractionation schedules for EGSCC have changed dramatically over the past decade. The relative benefits of hypofractionation and hyperfractionation need to be balanced against the OTT and inconvenience with which these approaches are associated. hyperfractionation has the advantage of shortening the OTT over CF and hypofractionation. On the other hand, the advantages of hypofractionation are not only shortened OTT but also reduced medical costs, frequency of patient visits, equipment burden, and staff labor. Consequently, hypofractionation has gained favor in recent years because this schedule is more advantageous for both patients and staff. Therefore, the use of hyperfractionation and CF at our Institution have been decreasing over the past few years (Figure 1), which is consistent with a study in the United States that showed increased use of hypofractionation for EGSCC over the years, with more than half of patients choosing it recently (10, 23). Moore *et al*. and consensus guidelines strongly recommend hypofractionation as the standard of care. The finding of significant public health cost savings by Moore *et al*. is an additional benefit of treatment with hypofractionation (24).

There were some limitations to our study because of its single-institution and retrospective nature. The number of patients was small and the selections of the RT options in the patients were not randomized. Additionally, a number of patients received chemotherapy concurrently with RT. Consequently, because selection bias may have occurred, care is needed in interpreting the study results. To confirm our results, it is important to continue to treat and evaluate greater numbers of patients and to report longer term follow-up data.

In conclusion, there were no significant differences in LC and OS between the three fractionation schedules. Our findings confirmed the utility of AFS in standard clinical practice and support its use for patients with EGSCC.

Conflicts of Interest

The Authors declare that they have no conflicts of interest regarding this study.

Authors' Contributions

GS designed the study, contributed to data acquisition, and prepared the article. HY performed statistical analyses and reviewed the article. GS, YS, AA, HY, NA, KM, DS, TK, TN, KK, SN, YY, SW, and KM contributed to data acquisition. HY, SH, and KY supervised the study. All Authors have read and approved the final article.

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