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Hypofractionated Radiotherapy for Stage I Squamous Cell Carcinoma Glottis: An Experience with 60Gy in 20 Fractions

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ABSTRACT

Introduction: Early-stage glottic cancer has a high cure rate with definitive radiotherapy. Historical reports show excellent local control. The present study evaluated the outcomes of early glottic cancer patients treated with a hypofractionated radiotherapy schedule of 60Gy in 20 fractions.

Material and Methods: This is a retrospective study of patients with stage I glottic cancer who received radical intent LINAC-based hypo-fractionated 3D conformal radiotherapy with a dose 60Gy in 20 fractions. The primary objective was to assess the locoregional control (LRC), and secondary objectives were to determine disease-free survival (DFS), overall survival (OS), and toxicity.

Results: The analysis included 105 patients from the age range of 35-88 years. About 69% of patients were over 60 years of age. The median overall treatment time (OTT) was 26 days (24 – 30 days). The mean follow-up was 74 months, ranging from 9 to 135 months. Seven patients had locoregional recurrence after an initial complete clinical response. Six had local, and one had a regional nodal recurrence. DFS at five years and ten years were 83% and 69%, and OS at five years and ten years were 87% and 80%, respectively. Most patients reported grade I skin reactions and tolerated the treatment well. We did not observe any late adverse events such as persistent laryngeal edema or radiation necrosis.

Conclusion: The radiotherapy schedule of 60Gy in 20 fractions over four weeks offers comparable local disease control with reasonable long-term side effects in T1 glottic cancer.

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Introduction

Laryngeal cancer is the most common head and neck cancer worldwide, with an annual incidence of 184,615 and mortality of 99840. It is the eleventh most common cause of cancer in India, with a national incidence of 34687 (2.6%) new registered cases and 21660 (2.5%) reported deaths [1]. Glottic cancer, which involves the vocal cord proper, is the most common among laryngeal cancers and is characterized by a high cure rate with early-stage detection and treatment. The treatment approach to early glottic cancer (T1-T2 N0) includes radiation therapy (RT), laser microsurgery, and conservative laryngeal surgery. The local control rate with definitive RT is excellent, 83–95% for T1 and 70-80% for T2 glottic cancer, [2-4] without an increase in normal tissue toxicity [5-7] and better or equivalent voice outcome [8-10]. Hence, RT is the preferred primary treatment worldwide, though laser microsurgery looks promising in selected patients [10-13].

The clinical target volume (CTV) for RT is confined to the larynx alone because of the sparse lymphatic drainage of the glottis. The dose and fractionation schedules vary broadly among different institutions, and there is no agreement regarding the ideal dose schedule. Hypofractionated RT is preferred in most centers as it reduces the overall treatment time [14]. The radiotherapy schedule, 60 Gy in 20 fractions, used in this study is unique as there is no published data available with this schedule and hence, we share our institutional clinical experience. The primary objective was to assess the locoregional control (LRC) of T1N0 glottic cancer patients who received a total dose of 60Gy, with 3Gy per fraction. The secondary objectives were to estimate disease-free survival (DFS), overall survival (OS), and toxicity.

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Materials and Methods

Study design

This is a retrospective study conducted in the department of radiation oncology at a tertiary care hospital, India. All stage I glottic squamous cell carcinoma patients who received radical intent hypofractionated 3D conformal radiotherapy [3DCRT] with the dose 60Gy in 20 fractions between January 2009 and December 2015 were included in this analysis. The data were retrieved from hospital medical records and radiation treatment plans. This study was approved by the institutional ethics committee [ECASM-AIMS-2021-326].

Technical and treatment information

CT simulation was done in the supine position with an extended neck, immobilized with a head and shoulder thermoplastic mask, comfortable headrest, and shoulder traction. 3DCRT was delivered by Linear accelerator (Elekta Precise Digital, Sweden) with lateral or oblique wedged pair fields, using 4 MV or 6 MV photons. The clinical target volume (CTV) included the entire larynx. The craniocaudal extend of the radiation portal was from the superior aspect of the thyroid cartilage to the lower end of the cricoid cartilage. The posterior border was at 1 cm posterior to the posterior border of the thyroid cartilage, and the anterior border flashed well over the skin. All patients received a dose of 60Gy in 20 fractions with 3Gy per fraction, five days a week, over four weeks with a calculated tumor biological effective dose [BED] of 78Gy.

Evaluation

Toxicity was evaluated according to RTOG Toxicity Scales. Patients were followed up periodically with clinical examination and video laryngoscopy. They had a computed tomography or PET scan to rule out recurrence when clinically suspected.

Locoregional recurrence refers to the recurrence of cancer (of the same histology) at the same site as the original (primary) tumor or the regional lymph nodes after a disease-free period. DFS refers to the duration from the date of commencement of RT till the first disease event or the last follow-up. OS refers to the course of time from the date of diagnosis till the last day of follow-up or date of death.

Statistical details

Statistical analysis was done using IBM SPSS 20(SPSS Inc., Chicago, USA). For all continuous variables, the results are given in Mean ± SD, whereas for all categorical variables they are given in numbers and percentages. The chi-square test was applied to obtain the association of categorical variables. Kaplan Meier estimates were used to calculate survival curves. All patients were included in the analysis. Kaplan Meier curves were constructed for time to recurrence and progression, and differences between groups were compared using the log-rank test. A p-value < 0.05 was considered statistically significant.

Results

The data of 105 patients with stage I glottic cancer who received hypofractionated RT with a dose of 60Gy in 20 fractions between January 2009 and December 2015 were analyzed. (TABLE 1). About 69% of patients were over 60 years of age. 99(94%) patients were males, and 6 (6%) were females. 51% of patients reported tobacco smoking habits. Regarding the stage, 87(83%) patients were T1aN0 and 18 (17%) were T1bN0. Anterior commissure involvement was seen in 51 (48%) patients.102 (97%) patients were treated with 4MV photons and others with 6MV.

A 0.5 cm thick bolus was used in the first 12 fractions of 88% of patients, including all cases with anterior commissure involvement. The median overall treatment time (OTT) was 26 days (range of 24 – 30 days). The mean follow-up was 74 months, ranging from 9 to 135 months or until death.

At the time of analysis, 89 patients were alive and disease free. Sixteen patients were dead. Three patients died due to disease, five to second primary cancer, and 8 to other reasons. Thirteen patients were diagnosed with second cancers on follow-up.

Locoregional recurrence

Seven patients had locoregional recurrence after an initial complete clinical response. Six had local, and one had a regional nodal recurrence. Five patients underwent salvage surgery and two were disease-free at the evaluation time. (TABLE 2)

Disease-free survival (DFS)

DFS in T1N0 glottic cancer patients receiving 60Gy in 20 fractions at five years and ten years were 83% and 69%, respectively. On subgroup analysis, the five-year and ten-year DFS of T1aN0 were 84.2% and 70.3%, and the same for T1bN0 were 84.7% and 70.6%, respectively. Patients with AC involvement had a DFS of 81.6% and 57.1% at five years and ten years, respectively, of which T1a had 82.5% and 56.9%, and T1b had 80% and 60%, respectively. DFS excluding the patients who developed second cancers were 89% and 81% at five years and ten years, respectively. (Figure 1)

Overall survival (OS)

TIN0 glottic cancer patients reported an OS of 87% and 80% at five and ten years, respectively. On subgroup analyses, the five and ten years OS of T1aN0 were 88% and 83%, and the same for T1bN0 were 83% and 69%, respectively.

Those with AC involvement had an OS of 85% and 74% at five years and ten years, among which T1a had 88% and 82% and T1b had 78% and 59%, respectively. (Figure 2) (TABLE 3)

Table 1. Baseline demographics and clinical characteristics of all patients with T1N0M0 laryngeal squamous cell carcinoma

Total Number	105 patients
Age	
• Range	35- 80 years
• < 60 years	33 (31.4%)
• >60 years	72 (68.6%)
Gender	
• Male	99 (94%)
• Female	6 (6%)
Site	
• Right vocal cord	57 (54.2%)
• Left vocal cord	30 (28.5%)
• Bilateral involvement	18 (17.14%)
• Anterior Commissure involvement	51 (48%)
Stage	
• T1aN0	87 (82.85%)
• T1bN0	18 (17.14%)
Radiation Details	
Energy	
4MV	102 (97%)
6MV	3 (3%)
Bolus	
Yes	92 (87.6%)
No	13 (12.4%)
Beam Orientation	
Right and left lateral	10 (9.52%)
Right and left Anterior Oblique	95 (90.47%)

Table 2. Clinical outcomes of all patients with T1N0M0 laryngeal squamous cell carcinoma treated with 60Gy in 20 fractions

Total	105
Alive	89
Dead	16
Recurrence	7
Local Recurrence	6
Nodal Recurrence	1
Alive without disease	82
Alive with second primary index disease cured	7
Dead due to disease	3
Dead due to unknown /other causes	8
Dead due to second primary index disease cured	5

Toxicity

At the time of completion of radiation treatment, 85% of patients had grade I skin and pharyngeal mucosal reactions. One patient had Grade III mucositis, and two had grade III skin reactions. Patients tolerated the treatment well, and unscheduled interruption was seen only in one patient. No late adverse events such as persistent laryngeal edema or radiation necrosis were reported.

Second malignancy

On follow-up, 13 patients were diagnosed with second malignancy, of which three patients developed it in the head and neck, and 10 had it in other regions like lung, breast, gastrointestinal and genito-urinary sites.

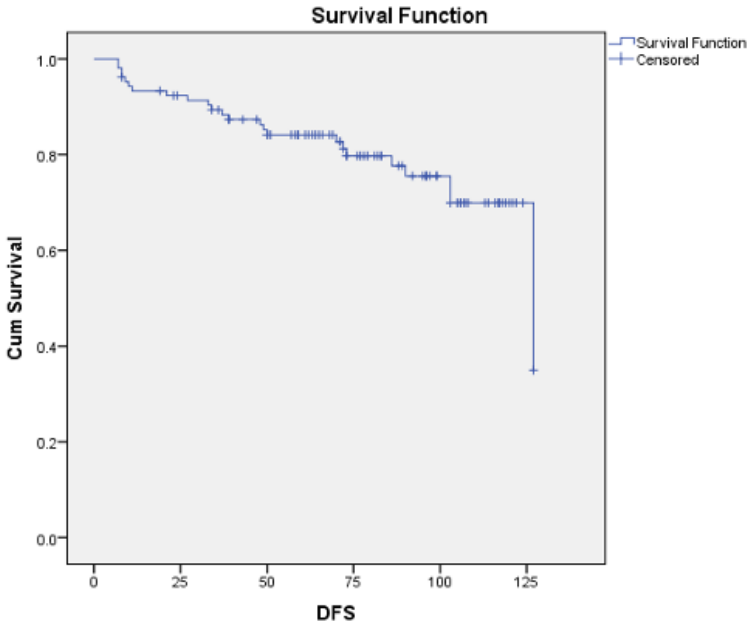

Figure 1. Disease-Free Survival. Disease-free survival [DFS] all patients with T1N0M0 laryngeal squamous cell carcinoma treated with 60Gy in 20 fractions. The 5 Year and 10 Year DFS is 83% and 69%, respectively.

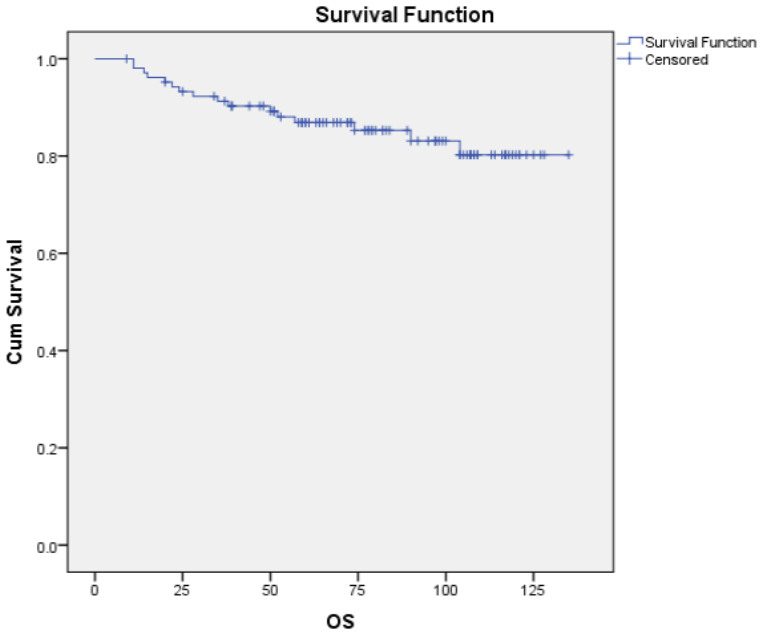

Figure 2. Overall Survival. Overall survival [OS] in all patients with T1N0M0 laryngeal squamous cell carcinoma treated with 60Gy in 20 fractions. The 5 Year and 10 Year OS is 87% and 80%, respectively

Table 3. Disease-free survival [DFS] and Overall Survival [OS] of all patients with T1N0M0 laryngeal squamous cell carcinoma treated with 60Gy in 20 fractions

Stage	DFS		OS	
	5 YEARS	10 YEARS	5 YEARS	10 YEARS
T1N0M0	83%	69%	87%	80%
T1aN0M0	84.2 %	70.3%	88%	83%
T1bN0M0	84.7%	70.6%	83%	69%

Discussion

Dose fractionation and overall treatment time play a significant role in the outcomes of radical radiotherapy for early glottic cancer. Hypofractionation is considered an appropriate strategy here, as the target volume is minimal [15-19]. As per the Linear- Quadratic (LQ) model, SCC of the head and neck generally is thought to have a high α / β ratio and thereby a low fractionation sensitivity. Most glottic tumors are usually well to moderately differentiated and slow-growing. It may contain a low proportion of cells with a relatively low α / β ratio. Also, laryngeal carcinoma is considered to have a shorter potential doubling time, hence a greater tendency for accelerated repopulation during radiotherapy than other head and neck SCC [5, 20].

Only a few randomized studies compare radiation schedules to treat early laryngeal cancer. In the landmark trial by Yamazaki et al. for stage I disease, the 5-year local control rate [LCR] was 77% for the conventional fractionation arm (60–66 Gy with 2.0 Gy daily) and 92% for the hypo-fractionation arm (56.25–63 Gy with 2.25 Gy daily; p = 0.004). This study proved that using a hypofractionated radiation regimen (2.25 Gy per fraction) with shorter OTTis superior to conventional fractionation (2 Gy per fraction), concerning local control without increasing the toxicity[21].

The Korean Radiation Oncology Group (KROG-0201), in another randomized controlled trial, compared 66 -70Gy in 2Gy per fraction with hypo-fractionated arm of 63-67.5Gy in 2.25Gy per fraction for T1 and T2 laryngeal cancers. As this study failed to accrue patients, it was closed prematurely. Analysis of 156 of the planned 282 patients showed a 5-year local progression-free survival of 77.8 % versus 88.5 %, which was not statistically significant [22].

Several hypofractionated studies for early laryngeal cancer radiotherapy use>3Gy/fraction. Gowda et al. have described the experience with three weeks of radiation therapy using hypofractionated schedules of 50-52.5Gy in 16 fractions. The five-year local control and OS were 93% and 80%, respectively[4]. Cheah et al. reported similar locoregional control rates of 88% and OS of 76% at five years with RT dose of 50 Gy in 16 fractions over 21 days.[23] Laskar et al. published a retrospective audit of patients treated with four hypofractionated schedules (50 Gy/15 fractions, 55 Gy/16 fractions, 60 Gy/24 fractions and 62.5 Gy/25 fractions).

Table 4. Biological Effective Dose (BED) and Equivalent total doses in 2-Gy fractions (EQD2) comparison for late reacting tissue, α/β ratio 3 Gy

DOSE	BED	EQD2
6000cGy / 20 Fractions	120	72
7000cGy / 35 Fractions	117	70

The patients were categorized into two groups of < 3 Gy or > 3 Gy per fraction. In this study, the local control and overall survival at ten years were 84 and 86.1%, respectively [13].

Hypofractionation thereby facilitates a substantial reduction in OTT, which may favorably influence disease control by minimizing the impact of accelerated repopulation. A shorter fractionation schedule reduces the machine load and saves valuable treatment time [4,24].

The BED was calculated using the standard linear quadratic equation [5,20],

$$BED = D\,(1+d/\,\alpha/\beta) \quad (1)$$

[For late responding tissues, α/β = 3Gy]

Accordingly, the schedule of 60Gy in 20 fractions over 26 days can be compared to the conventional fractionated schedule of 70Gy in 35 fractions over 46 days for the log10 cell kill and late-effect BED. (TABLE 4)

In our study population, disease-free survival (DFS) and overall survival (OS) at five years and ten years were comparable to those published in the literature. No severe late adverse events such as persistent laryngeal edema or radiation necrosis were reported with this schedule.

Although AC involvement has been linked as a poor prognostic factor for LCR in many studies, our study did not identify such a correlation [3, 25]. Moreover, recurrences were observed only in a tiny group (7 out of 105). Stringent follow-up was beneficial because most recurrences were detected early and could be salvaged. A second malignancy was detected on follow-up in 13 out of 105 patients, almost double the number of locoregional failures observed.

This study is one of the more extensive series of patients with T1 glottis, treated with LINAC-based 3DCRT using 4MV photons. The radiation schedule used is unique and the survival outcomes are reasonable.

A potential limitation of this study is its retrospective nature and inherent biases. Though most patients had good laryngeal function post-radiation, the study did not objectively evaluate voice quality before and after treatment.

Conclusion

Hypofractionated radiotherapy schedules appear effective in curing stage 1squamous cell carcinoma glottis. The optimum OTT, fraction size, and dose are yet to be recognized and more extensive prospective clinical trials are warranted. The schedule of 60Gy in 20 fractions over four weeks offers comparable local disease control with reasonable long-term side effects.

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