

# Hypofractionated (2.75 Gy per fraction) versus Conventionally Fractionated Primary Radiotherapy for T2N0M0 Carcinoma of the Glottis

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## Abstract

**Introduction** Radiotherapy provides excellent outcome in early stage glottic cancer; however, the optimal radiotherapy dose fractionation remains unknown.

**Objective** To investigate the outcome of patients with T2N0M0 treated with either hypofractionated (HypoFxn) or conventionally fractionated radical (ConFxn) radiotherapy.

**Methods** According to our institutional protocol, patients with T2N0M0 glottic cancer can be treated either with ConFxn or HypoFxn radiotherapy, as per clinician's and patient's choice, following shared decision making discussing the advantages and disadvantages of both modalities. A total of 77 patients with T2N0M0 squamous cell carcinoma of glottis treated with either HypoFxn 55Gy in 20 fractions ( $n = 19$ ) or ConFxn 63 to 65Gy in 30 fractions ( $n = 58$ ) were included.

**Results** With median follow-up of 3.4 years, there was no significant difference in disease-free survival (median: HypoFxn = 65.2 months, and ConFxn = 75.3 months;  $p = 0.874$ ), local recurrence free survival rates (median: HypoFxn = 78.8 months vs. ConFxn = 81.2 months;  $p = 0.274$ ), and overall survival (median: HypoFxn = 65.9 months vs. ConFxn = 67.7 months;  $p = 0.532$ ). Elective neck irradiation was given to 43 patients, all in the ConFxn group, and this was associated with poorer local control ( $p = 0.027$ ). The use of radiotherapy modality, three-dimensional conformal radiotherapy (3DRT) versus intensity modulated radiotherapy (IMRT), was not a prognostic factor ( $p = 0.36$ ). In the HypoFxn group, grade III acute dysphagia requiring nasogastric tube was 16%, compared with 25% in the ConFxn group ( $p = 0.446$ ).

**Conclusion** HypoFxn radiotherapy provides a comparable treatment outcome with acceptable toxicity. The addition of prophylactic irradiation of the neck lymph nodes has no impact on regional control.

## Keywords

- ▶ T2N0M0
- ▶ glottis
- ▶ larynx
- ▶ radiotherapy
- ▶ hypofractionated

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## Introduction

Laryngeal cancer is one of the most common cancers of the head and neck region, and the true vocal cords or glottic larynx are the most commonly involved site, making up approximately  $\frac{2}{3}$  of all laryngeal cancers.<sup>1</sup> The term *early stage glottic cancer* constitutes T1-T2N0M0 and it typically presents early. Due to lack of lymphatic drainage in the glottic mucosa, there is relatively small risk of lymph nodal involvement.<sup>2</sup> As per the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system 7<sup>th</sup> edition, T2 carcinoma of glottis was defined as a tumor extending to the supraglottis or subglottis, or with impaired mobility of the vocal cords. For early stage glottic cancer, the treatment options are either surgery or radiotherapy. There remains insufficient evidence to determine which of these treatment options is superior to the other.<sup>3</sup> Irrespective of treatment modality, the survival rate is high.

In most of the published studies, the patient population is a mixture of T1 and T2, labeled as *early stage glottic cancer*. Therefore, little is known exclusively about the outcome of the T2N0M0 disease. As far as the optimal radiotherapy dose fractionation is concerned, there is a lack of level one evidence. Theoretically, there is advantage of using hypofractionated radiotherapy with short overall treatment time (OTT) which may improve tumor control by minimizing tumor repopulation. However, there is no consensus on the definition of optimal hypofractionated radiotherapy. A recent National Cancer Database analysis involving more than 10,000 patients with T1-T2N0M0 glottic cancer showed that the use of hypofractionated radiotherapy (2.25 Gy/fraction to 63–65.25 Gy) increased over the period studied, with improved survival rates when compared with conventional radiotherapy (2.0 Gy/fraction to 66–70 Gy).<sup>4</sup> Another recent, single-center analysis showed a fraction size of 2.25 Gy provided acceptable disease control rates in this patient population.<sup>5</sup> To date, the majority of the published studies of hypofractionated radiotherapy in early glottic cancer included a mostly T1 patient population treated with < 2.5 Gy per fraction.<sup>6–12</sup>

The primary aim of this study was to analyze the survival outcomes of radical radiotherapy for T2N0M0 carcinoma of the glottis and compare two radiotherapy regimens: fractionated radiotherapy of 63 to 65 Gy in 30 daily fractions (2.10–2.17 Gy per fraction) and hypofractionated radiotherapy of 55 Gy in 20 daily fractions (2.75 Gy per fraction). The secondary aims were to analyze the toxicity data and the effect of prophylactic neck irradiation in this disease group.

## Materials and Methods

### Patient Population

Between January 2010 to December 2016 (7-year period), data were collected from 77 patients with T2N0M0 carcinoma of the glottis treated with primary radiotherapy. All patients had clinical examination, including laryngoscopy +/- examination under anesthesia, histology confirmation of squamous cell carcinoma, were fully staged (TNM 7<sup>th</sup>

edition) using contrast-enhanced computed tomography (CT) of the neck and chest. All patients had a World Health Organization performance status (WHO PS) of 0 to 2.

Patients underwent a shared decision-making process with their assigned physician and information was provided so that they could make a fully informed decision as to whether they chose the conventional or hypofractionated radiotherapy treatment.

### Radiotherapy

All patients had a customized immobilization mask made and a planning computed tomography (CT) scan comprising 3 mm slices from 2 cm above the base of skull to 3 cm below the jugular notch of manubrium. Taking clinical and radiological information into account, a gross tumor volume (GTV) was drawn on each slice. It was then grown circumferentially of 5 to 10 mm as a help structure for the clinical target volume (CTV), which was then expanded to include the entire larynx. The CTV was edited for anatomical barriers such as bone. Thyroid gland and carotid arteries were not included in the CTV unless these organs were within 5 to 10mm of the GTV. An isotropic margin of 5 mm for three-dimensional conformal radiotherapy (3DRT) or 3 mm for intensity modulated radiotherapy (IMRT) was added to define the planning target volume (PTV).

Until March 2015, treatment was delivered using 3DRT ( $n = 37$ ). Following this period, radiotherapy was delivered initially with step-and-shoot IMRT (from March 2015 to September 2017) and later with volumetric modulated arc radiotherapy (VMAT,  $n = 40$ ).

There were 19 patients treated with the hypofractionated radiotherapy (HypoFxn), with 55 Gy in 20 daily fractions (2.75 Gy per fraction) over a 4-week period. For 58 patients, the treatment used was conventionally fractionated radiotherapy (ConFxn) with 63 to 65 Gy given in 30 daily fractions (2.10–2.17Gy per fraction) over a 6-week period. In all patients who received hypofractionated radiotherapy, there was no elective neck irradiation; however, in 43 of the 58 patients treated with conventionally fractionated radiotherapy, a prophylactic dose of 54Gy in 30 fractions was used to treat the neck electively. The decision to treat the neck with elective irradiation was based on the clinician's choice and was available in our protocol at that time; if chosen, radiotherapy was given bilaterally. All patients managed to complete their radiotherapy course.

### Clinical Assessments

During radiotherapy, all patients were assessed on a weekly basis by a head and neck multidisciplinary team including a doctor, head and neck cancer specialist nurse, dietitian, speech and swallowing therapist, and oral hygienist. Toxicities were graded as per common toxicity criterion. At 6 and 12 weeks after radiotherapy, all patients were examined in a head and neck surgical clinic, including laryngoscopy, and their response to radiotherapy was documented. Patients were then regularly followed up with a 8-weeks interval during the 1st year posttreatment, and 3 to 4 monthly follow-up visits in years 2 to 5 of follow-up. In case of clinical

suspicion of recurrence, we performed CT scans, ultrasounds of neck +/- fine needle aspiration, or a positron emission tomography-computed tomography (PET/CT) scan. Voice evaluation was completed using the Voice Handicap Index-10<sup>13</sup> auditory perceptual measure pretreatment and three-months postradiotherapy to assess quality of voice. As per Arffa et al.,<sup>14</sup> an increase in VHI-10 score by > 11 posttreatment from the baseline was considered as abnormal, which meant the voice was not preserved.

### Statistical Analysis

The patients were placed in two groups, HypoFxn and ConFxn. A *t*-test was performed to compare the two groups and a *p*-value of < 0.05 was considered statistically significant. Survival rates were estimated using the Kaplan-Meier curve.

### Ethical Consideration

This is a retrospective study, registered with a local hospital clinical effectiveness and register as a service review project. The registration reference number was 9699.

### Results

This study's cohort (*n* = 77) was comprised of 69 men and 8 women. The mean age was 67.3 (range 45–91, SD 10.6). According to the WHO PS, 36 patients had grade zero, 34 patients had PS one, and the remaining 7 patients had PS two. Furthermore, 21 patients presented with supraglottic extension, 19 patients with a subglottic extension, 6 patients had both supraglottic and subglottic extension, and in the remaining 31 patients we identified a bulky tumor which was limited to the vocal cords but was causing impaired mobility.

Comparing the two groups, there were 19 patients in the HypoFxn group and 58 in the ConFxn group. The patients in the ConFxn group were slightly younger than those in the HypoFxn group; however, this difference was not statistically significant (mean age 66.3 years vs. 70.4 years; *p* = 0.906). In the HypoFxn group, 74% of patients had WHO PS 0 or 1. This level of functioning capacity was significantly lower than that in the ConFxn group, in which 93% patients had WHO PS 0 or 1 (*p* = 0.002). The median OTT in the HypoFxn group was 27 days (range 26–29) as compared with a median 41 days in the ConFxn group (range 38–42). In the HypoFxn group, all patients had a complete response to treatment, while in the ConFxn group, all but 2 patients had complete response; this small difference was not statistically significant (*p* = 0.412). In the HypoFxn group, there were two local recurrences (10%) and both patients were treated successfully with laryngectomies. In the ConFxn group, there were 12 recurrences (21%) out of 56 patients who responded to radiotherapy; and 10 patients in this group underwent salvage laryngectomies, including the two patients who didn't respond to primary radiotherapy. The remaining 4 patients were deemed unfit for salvage surgery and had best supportive care. The difference in recurrence rates between the two groups was not statistically significant (*p* = 0.412). In our study, involvement of supraglottis or sub-

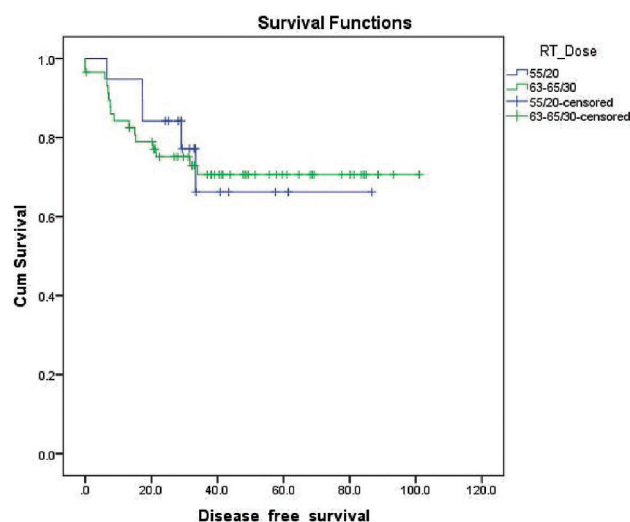


Fig. 1 Kaplan-Meier estimate for disease free survival.

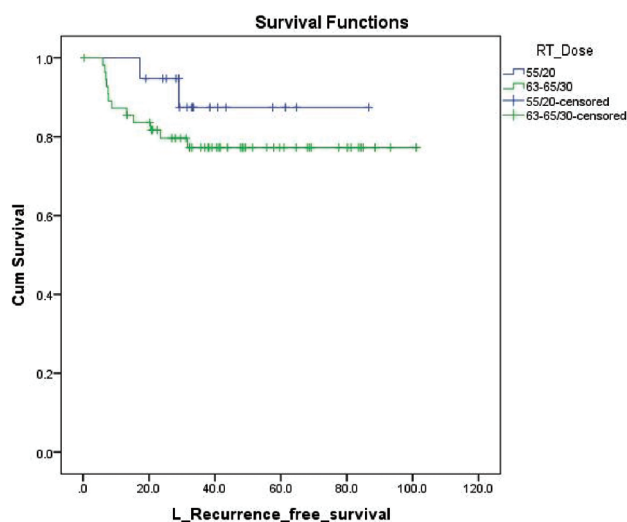
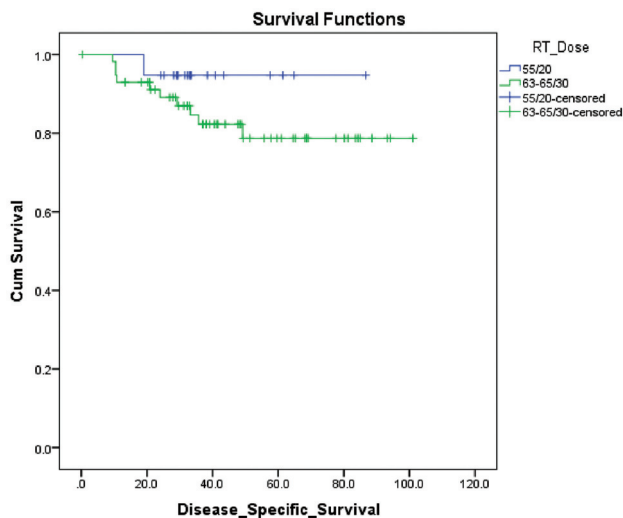


Fig. 2 Kaplan-Meier estimate for local recurrence free survival.

glottis was not prognostically significant (*p* = 0.266 for disease free survival, DFS; *p* = 0.552 for local recurrence free survival rates; and *p* = 0.486 for overall survival, OS).

With a median follow-up of 3.4 years, there was no significant difference in DFS between the two groups (median: HypoFxn = 65.2 months, 95% CI 49.2–81.3, vs. ConFxn = 75.3 months, 95% CI 64.6–86.0; *p* = 0.874) [►Fig. 1], local recurrence free survival (LFRS) rates were similar as well (median: HypoFxn = 78.8 months, 95% CI 68.6–89.1, vs. ConFxn = 81.2 months 95% CI 71.2–91.2; *p* = 0.274) [►Fig. 2]. Disease specific survival (DSS) was also similar between the two groups (median: HypoFxn = 83.1 months, 95% CI 76.3–89.9, vs. ConFxn = 85.2 months, 95% CI 76.3–94.1; *p* = 0.254), as well as OS (median: HypoFxn = 65.9 months, 95% CI 50.3–81.5, vs. ConFxn = 67.7 months, 95% CI 57.7–77.7; *p* = 0.532) [►Fig. 3]. These results are summarized in ►Table 1.



**Fig. 3** Kaplan-Meier estimate for disease specific survival.

The 2- and 5-year LRFs rates were 94.7% and 87.4% in the HypoFxn group versus 79.6% and 77.3% in the ConFxn group, but this difference was not significant ( $p = 0.274$ ). In total, 5 patients (7%) developed distant metastases, 2 patients in the ConFxn and 3 in the HypoFxn group. Of the 5 cases of distant metastases, 2 developed mediastinal lymphadenopathy, and the remaining three developed lung metastases. In total, 31 patients died; with 11 having died of carcinoma of glottis and 20 of other causes.

Examining treatment-related toxicities, 14 patients (73%) in the HypoFxn group developed dysphagia of any grade (I–III), which is higher than the 35 of 55 patients (64%) in the ConFxn group (there were data missing from three patients of the ConFxn group). This difference was not significant ( $p = 0.425$ ). In the HypoFxn group, 3 patients (16%) developed grade III acute dysphagia requiring nasogastric (NG) tube, while the incidence was 25% (14/55 patients) in the ConFxn group; the difference was not significant ( $p = 0.446$ ). There was no significant difference in incidences of other acute toxicities in the two groups (► **Table 1**). One patient in the ConFxn group developed a grade IV, acute skin reaction. There was no registered grade V toxicity. In terms of late toxicities, 1 patient (5%) in the HypoFxn and 5 patients (9%) in the ConFxn group developed a grade III upper esophageal stricture but the difference was not significant ( $p = 0.636$ ). There was no significant difference in voice preservation outcomes of the two groups; using the VHI-10 score, the voice was preserved in 84.2% of patients treated with HypoFxn versus 72.4% treated with ConFxn ( $p = 0.301$ ).

Elective neck irradiation was performed in 43 patients (all in the ConFxn group). Neck recurrence developed in a total of 8 patients in both groups. Out of these 8 patients, 5 had elective neck irradiation and the remaining 3 developed regional recurrence, all of whom had no prophylactic radiotherapy to the neck. Although the numbers are small, this difference was significant ( $p = 0.027$ ) suggesting that neck irradiation versus no neck irradiation in T2N0M0 was associated with worst local control (LC). The radiotherapy mo-

dality (3DRT versus IMRT) was not a prognostic factor ( $p = 0.36$ ).

## Discussion

The role of radiotherapy in the treatment of early stage glottic cancer is well established. Although both radiotherapy and surgery are equally effective treatment modalities concerning survival, speech and voice outcomes are significantly better in patients treated with radiotherapy.<sup>15</sup> Both OTT and fractionation have a crucial role in the outcome of early glottis carcinoma. In a randomized trial by Yamazaki et al.,<sup>6</sup> the authors confirmed the positive effect of short OTT and higher dose per fraction on LC and disease specific survival for T1N0M0 early stage glottic cancer. In a randomized trial by Moon et al.,<sup>7</sup> 82 patients received ConFxn (66 Gy/33 fractions for T1 and 70 Gy/35 fractions for T2), and 74 patients received HypoFxn (63 Gy/28 fractions for T1 and 67.5 Gy/30 fractions for T2). Elective lymph nodal irradiation was not allowed. For T1a disease, 5-year local progression-free survival (PFS) was significantly better for HypoFxn. The number of patients with T2 disease was quite low, 8 in the ConFxn group and 9 in the HypoFxn group. The 2- and 5-year local PFS rates for patients with T2 disease varied in the ConFxn group (75.0% and 56.3%, respectively) and stayed the same in the HypoFxn group (77.8%), with HR 0.46 and  $p = 0.499$ . There was no difference in toxicity in the two treatment arms. Although this trial was closed early due to poor accrual, it did suggest the potential benefits of HypoFxn.

In a study by Stokes et al.,<sup>16</sup> the authors reviewed the National Cancer Database for T2N0M0 glottic carcinoma and analyzed the outcome of 3,333 patients treated with definitive radiotherapy. The most common radiotherapy fractionation used was ConFxn ( $n = 2006$ ), followed by HypoFxn ( $n = 1166$ ), and hyperfractionation ( $n = 161$ ). The analysis showed that altered fractionation was associated with improved survival. As compared with ConFxn, HypoFxn (HR 0.84, 95% CI 0.73–0.97,  $p = 0.017$ ), and hyperfractionation (HR 0.74, 95% CI 0.56–0.99,  $p = 0.044$ ) were associated with improved OS. This study also showed that there was a significant decline in the use of ConFxn (69.8–44.1%) and hyperfractionation (6.3–1.8%), and an increase in the use of HypoFxn (23.9–54.1%) ( $p < 0.001$ ).

Dixon et al.<sup>17</sup> published the outcome 112 patients with T2 glottic cancer treated with a HypoFxn accelerated radiotherapy dose of 52.5 Gy in 16 daily fractions (3.28 Gy per fraction). This HypoFxn regimen was well tolerated with excellent survival results. The 5-year OS was 67%, 5-year LC was 82%, and the 5-year DSS was 90%. Severe late toxicity scores were only 1.8%.

In a recently published study by Adeel et al.,<sup>18</sup> outcomes of patients with early stage glottis cancer treated with definitive radiotherapy were presented. Out of a total 242 patients, 31 patients were with T2 who were treated with 65 Gy radiotherapy. There were 8 local and 1 locoregional but no distant failures (26%). The 5-year OS and DSS were 67% and 71%, respectively.

**Table 1** A comparative analysis on patient demographics, disease characteristics and treatment outcomes of the two groups

Characteristic	HypoFxn (55 Gy in 20 fractions)	ConFxn (63–65 Gy in 30 fractions)	p-value
N	19	58	
Gender (male:female)	17:2	52:6	0.982
Age – mean with 95% CI	70.4 (65.5–75.3)	66.3 (63.5–69.1)	0.906
PS 0 1 2	4 10 5	32 24 4	0.002 (better PS in > 60 group)
OTT – median days	27 (26–29)	41 (38–42)	Inherently different groups, so no statistics
Response to RT	100%	96.6%	0.412
LR	2/19	12/56 (2 non responders were excluded)	0.292
Requiring laryngectomy	2	10 (out of 58)	0.484
Dysphagia (G0–1:2–3)	5:14	20:35 (missing data in 3)	0.425
NG tube requirement	3	14 (out of 58)	0.446
Acute toxicities – other (G0– 1: 2–4)	7: 12	19:36 (missing data in 3)	0.857
Late toxicity (G0:1–3)	15:4	46:12	0.973
Stricture	1	5	0.636
Voice preservation – yes No	16 3	42 16	0.301
Admission hospital	3	13	0.537
DFS – median with 95%CI	65.2 months (49.2–81.3)	75.3 months (64.6–86)	0.874
LRFS – median with 95%CI	78.8 months (68.6–89.1)	81.2 months (71.2–91.2)	0.274
DSS – median with 95%CI	83.1 (76.3–89.9)	85.2 (76.3–94.1)	0.254
OS – median with 95%CI	65.9 (50.3–81.5)	67.7 (57.7–77.7)	0.532

**Abbreviations used:** ConFxn, conventionally fractionation; DFS, disease free survival; DSS, disease specific survival; G, grade; Hb, haemoglobin; HypoFxn= hypofractionated group; LR, local recurrence; LRFS, locoregional disease free survival; n, number; NG, nasogastric; OS, overall survival; OTT, overall treatment time; PS, performance status.

Frata et al.<sup>19</sup> published outcomes for 256 patients with T2N0M0 glottic cancer treated with radiotherapy. The 3-year, 5-year, and 10-year OS rates were, respectively, 73%, 59%, and 37%. Corresponding values for cumulative LC probability were 73%, 73%, and 70%; for DSS, the rates were 89%, 86%, and 85%, taking into account surgical salvage of relapsed cases. Regarding dosage, 13% of the patients received < 61 Gy, 32% were treated with 61 to 65 Gy, and the remaining 55% received > 65 Gy radiotherapy. As far as radiotherapy fraction dose was concerned, 55% received ≤ 2 Gy per fraction, 41% received 2.1 to 2.4 Gy per fraction, and only 4% patients were treated with > 2.4 Gy per fraction. Both total radiotherapy dose and fraction dose were not statistically significant.

Sert et al.<sup>20</sup> published their experience of patterns of failure in early stage glottis cancer patients treated with definitive radiotherapy. There were 22 patients with T2N0M0 disease, treated with a dose of 65.25 Gy in 29 fractions. No prophylactic neck radiotherapy was employed. Of these 22 patients, 8 patients had failures (5 had isolated local recurrences, 1 had isolated lymphatic recurrences, and 2 had concomitant local and regional lymphatic recur-

rences). The 5-year LC rates after radiotherapy were 56% but, taking salvage surgery into account, the 5-year LC rates were 75%. In their multivariate analysis, only advanced T stage (T1a vs. T1b vs. T2) was significantly affecting OS (90% vs. 86% vs. 49%, respectively,  $p = 0.023$ ).

There is no exact definition of HypoFxn. In the context of early stage glottic cancer, the literature as described above has shown various doses per fraction to define HypoFxn. It ranged from 2.25<sup>7</sup> to 3.28 Gy per fraction.<sup>17</sup> In our study, the dose per fraction used for ConFxn (2.17 Gy per fraction) was close to that used by Moon et al.<sup>7</sup> to define their HypoFxn. In our study, the dose per fraction used for ConFxn (2.17 Gy per fraction) was close to the dose per fraction used by Moon et al.<sup>8</sup> to define their HypoFxn. In our study, 2.75 Gy per fraction was used to define HypoFxn, and by specifying the definition of hypofractionation to ≥ 2.5 Gy per fraction, there are only few published studies – **Table 2**. In two studies where patients with T2N0M0 glottic cancer were treated with 55Gy in 2.75Gy per fraction, the 5-year local failure rates were ≥ 80%.<sup>12,21</sup> Our study had similar results. In an old study published in 1998, the 5-year relapse-free rates were

**Table 2** A tabulated summary of studies using hypofractionated ( $\geq 2.5$  Gy per fraction) radiotherapy in patients with T2N0M0 carcinoma of the glottis

Study with year of publication (in chronological order)	Type of study	Number of patients with T2N0M0	Radiotherapy dose	OTT	Outcome
Warde et al 1998 <sup>22</sup>	Retrospective	286	50 Gy in 20 f (2.5 Gy/f)	4 weeks	5-year relapse free rates 69%
Short et al 2006 <sup>12</sup>	Retrospective	43*	55 Gy in 20 f (2.75 Gy/f)	4 weeks	5-year LFC 81% which was not different to that treated with standard dose fractionation (80%, $p = 0.81$ ), 5-year LFC 92% vs 80% with standard RT ( $p = 0.29$ )
Ermis et al 2015 <sup>21</sup>	Retrospective	64	55 Gy in 20 f (2.75 Gy/f)	26 days	5-year LC 80.9%
Current study	Retrospective	77 (19 treated with Hypofractionated and 58 with conventional RT)	55 Gy in 20 f (2.75 Gy/f)	27 days	5-year LRFS 87.4% with hypofractionated and 77.3% with conventional RT ( $p = 0.274$ )

**Abbreviations:** f, fractions; LC, local control; LFC, laryngectomy free survival; LRFS, local recurrence free survival; OTT, overall treatment time; RT, radiotherapy. **Notes:** \*In this study, total number of patients with T2 disease was 43. No further information was available that out of these total 43, how many patients were treated with standard dose fractionation (60–66 Gy in 30–33 fractions) and how many with hypofractionated radiotherapy.

69% but it is important to note that the radiotherapy total dose was 50 Gy in that study, as compared with 55Gy in the other three studies ► **Table 2.**<sup>2,22</sup>

Based on previously published studies regarding radiobiology,<sup>23–26</sup> we have summarized the radiobiological calculation comparison of different radiotherapy regimens in ► **Table 3.** This comparison suggests a potential therapeutic gain for hypofractionation with 2.75Gy per fraction. As suggested by Ermis et al.,<sup>21</sup> hypofractionation is a particularly appealing strategy to treat early glottic cancer given the relatively small target volume.

In our study, the use of radiotherapy techniques (3DRT vs. IMRT, including VMAT) did not show any significant difference on outcome. This was consistent with a study by Cetinayak et al.<sup>27</sup> where use of VMAT showed no significant improvement over 3DRT but a trend toward better LC and DSS rates. In our study, the survival rates were similar to the ones reported in the literature, and HypoFxn showed no inferiority to ConFxn. The incidences of NG tube feedings in the ConFxn group were higher (25%) when compared with

the HypoFxn group (16%), though this difference was not statistically significant. This higher incidence of NG feeding in ConFxn could well be because 74% patients in this group also received elective nodal irradiation 54 Gy. In our study, implying neck irradiation was associated with worse LC ( $p = 0.027$ ) but there was a potential selection bias as more aggressive tumors were treated with neck irradiation and it is unlikely that neck irradiation in itself would cause worse oncological outcome.

Based on the above evidence, while also taking financial and logistic considerations into account, it has led to the adoption of HypoFxn as the schedule of choice for early stage glottis cancer.<sup>28</sup>

As far as addition of chemotherapy to radiotherapy is concerned, it is not recommended for stage II glottis cancer.<sup>29</sup> A recently published retrospective study reported better LC in patients with T2N0M0 glottis cancer treated with chemoradiotherapy as compared with radiotherapy alone (55.6% vs. 87.0%,  $p < 0.05$ ), though these results must be verified in a randomized prospective trial.<sup>30</sup>

**Table 3** BED calculation of radiotherapy regimens

Regimen	BED <sub>10</sub> for tumor	BED <sub>3</sub> for late effects
70 Gy in 35 daily fractions*	65.5	116.6 Gy
63–65 Gy in 30 daily fractions**	63.1 - 66.0	107.1–112.0 Gy
55 Gy in 20 daily fractions***	67.8	105.4 Gy

**Notes:** \*One of the most commonly used radiotherapy regimens in head and neck cancer. \*\*Conventional radiotherapy regimen used in our study. \*\*\*Hypofractionated radiotherapy regimen used in our study and in other two previously published studies.<sup>12,21</sup>

The tumor biologically effective dose (BED) was calculated as follows:

$$BED = D [1 + d/(\alpha/\beta)] - K(T - T_K)$$

In which: D = total dose (Gy); d = dose per fraction (Gy);  $\alpha/\beta$  = linear ( $\alpha$ ) and quadratic ( $\beta$ ) components of the linear quadratic model (Gy); T = overall treatment time (days);  $T_K$  = onset of accelerated repopulation time (days);  $K = 0.77$  Gy per day using parameters of  $\alpha = 0.3 \text{ Gy}^{-1}$  and  $T_p$  (average doubling time during accelerated repopulation) = 3 days;  $\alpha/\beta = 10 \text{ Gy}$ ;  $\alpha = 0.3 \text{ Gy}^{-1}$ ;  $T_K = 22$  days.

The formula for late effects is:

$$BED = D [1 + (d/\alpha/\beta)]$$

$$\alpha/\beta = 3 \text{ Gy}$$

## Limitations

Our study has a number of limitations. First, being a single-center retrospective study, it may have some bias including clinician and patient choice with regard to selection of treatment type, which caused some heterogeneity in the two treatment groups. Second, prognostically there was no further differentiation information present in terms of T2a or T2b disease. Third the data on patients' smoking status was not available for this study. Fourth, the number of patients in the HypoFxn group was smaller than in the ConFxn group, which may have introduced potential bias with a possible reduction in finding a difference between the two arms. However, the figures do reflect a real world scenario. Despite these limitations, we feel that our study provides useful information which adds to the knowledge of different radiotherapy dose fractions used in a single institute to treat this disease group.

## Conclusions

Accepting the present limitations, our study shows that hypofractionated radiotherapy provides a comparable treatment outcome with acceptable toxicity and a good functional outcome. Our study also shows that for this disease group, radiotherapy target field should be kept limited to larynx only; furthermore, the addition of elective irradiation of the neck lymph nodes has no impact on regional control and may lead to higher toxicity.

### Declaration

Part of this data was presented as an abstract poster at the American Society for Radiation Oncology (ASTRO) Multidisciplinary Symposium on Head and Neck Cancers 2020. This abstract was published in the Red journal as a supplement and can be assessed here; [https://www.redjournal.org/article/S0360-3016\(19\)34281-6/abstract](https://www.redjournal.org/article/S0360-3016(19)34281-6/abstract)

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### Conflict of Interests

The authors have no conflict of interests to declare.

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