Hypofractionated Radiotherapy of Early Glottic Cancer - A Single Institution Experience of 52.5 Gray in 15 Fractions among Patients Attending a Tertiary Care Center

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ABSTRACT

BACKGROUND

The standard conventional radiation schedule for early laryngeal cancer is 64 - 70 Gy in 2 Gy per fraction over 6.5 - 7 weeks. Hypofractionated radiotherapy in early laryngeal cancer allows delivery of larger dose per fraction (fraction size) in decreased overall treatment time with improved local control and similar survival rates. Reduction in treatment time also optimizes the usage of radiotherapy resources. The purpose of this study was to estimate the local control rates, survival rates and toxicity profile of hypofractionated radiotherapy of 52.5 Gy in 15 fractions for early glottic cancer.

METHODS

Twenty-eight patients with early glottic squamous cell carcinoma (SCC) treated with hypofractionated definitive radiotherapy from June 2015 to December 2019 were analyzed. The median age was 61 years. Total dose of 52.5 Gy in 15 fractions was delivered over three-four weeks with a fraction size of 3.5 Gy. The median follow-up period was 23.8 months.

RESULTS

The 5-year local control rates were 96.4 % with one recurrence. The 5-year overall survival rate was 100 % and cause specific survival at 5 years was 100 %. There was no association of T1 sub staging, T2 (P - 0.40) and no significant association of anterior commissure involvement (P = 0.408, chi square value = 3.982) and pre-treatment haemoglobin (P - 0.480) on local control. Late complications include laryngeal oedema (21.5 %), altered thyroid function (3.6 %), cardiac complication (3.6 %) and altered voice quality (14.3 %).There was no association of local control with field size (FS) (P = 0.812), beam energy (P = 0.098) overall treatment time of less than thirty days (P - 0.747).

CONCLUSIONS

Local control with hypofractionated radiotherapy for early laryngeal glottis squamous cell carcinoma is excellent with no severe complications. The short overall treatment time enables channelling of radiotherapy resources in low budget countries with long wait list for radiation.

KEYWORDS

Early Laryngeal Cancer, Glottic Cancer, Hypofractionated Radiotherapy, Overall Treatment Time.

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BACKGROUND

In India, laryngeal cancer is one of the ten leading cancers with an established relationship with tobacco smoking and contributing to 3 - 6% of all cancers in men.[1] The vocal cords (glottis) are the most commonly involved subsite. The characteristic feature of glottic cancer is the low risk of lymphatic spread attributable to the sparse lymphatic drainage of the glottic mucosa.[2] The aim of management are cure with laryngeal preservation and good voice quality.[3] The standard treatment options for early laryngeal glottis cancer (T1, T2 N0) include radiation or transoral laser microsurgery/open partial laryngectomy. Open partial laryngectomy is reserved for salvageable local recurrences in the present era.[3,4]

The standard conventional schedule is 64 - 70 Gy in 2 Gy per fraction over 6.5 - 7 weeks. The effective and recommend hypofractionated schedules are 54 - 55 Gy in 20 daily fractions over 4 weeks, 50 - 52.5 Gy in 16 daily fractions over 3 weeks[5] and 63 - 65.25 in 2.25 Gy per fraction over 5.6 - 5.8 weeks.[6,7]

Hypofractionated radiotherapy allows equivalent total dose to be delivered as larger dose per fraction (fraction size) in decreased overall treatment time that takes care of accelerated repopulation. Local control improves at the expense of increased late morbidity. The risk of late effects is greater with high radiation dose, large fraction sizes and larger treatment volumes. The main mechanisms thought to be responsible for the late effects of radiotherapy are the vasculature and connective tissue (stromal tissue) damage and reduced proliferative capacity of stem cells.[8] Small field size and decreased volume of mucosal irradiation in early laryngeal cancer almost nullifies the effect of large fraction size on late reacting tissues.[7,9]

The morbidity of a long-protracted course of radiation of 7 weeks and thereby the hospital stay or complications are reduced. Reduction in treatment time also optimizes the usage of radiotherapy resources. Most of the recurrences are salvaged by organ preserving surgeries like open partial laryngectomy. This improves the cause specific survival.

Organ preservation surgeries in early laryngeal cancer mandate anaesthetic procedures and considerable expertise to work in a small operative field, especially in those with distorted anatomy. Voice quality achieved with radiotherapy is better than surgery.

Our retrospective study was intended to derive the outcome of T1/T2 glottic cancer treated with 52.5 Gy in 15 fractions over 3 weeks and the impact of fraction size, field size, volume of mucosal irradiation, anterior commissural involvement, and subglottic extension on outcome. The primary objective was assessing loco regional control rates, survival rates and toxicity profile of this treatment protocol. Organ preservation rate and association of fraction size, field size, volume of mucosal irradiation, anterior commissural involvement, and subglottic extension on outcome were the secondary objectives of the study. The aim was to estimate the local control rates, survival rates and toxicity profile of hypofractionated radiotherapy of 52.5 Gy in 15 fractions for early glottic cancer.

METHODS

This single institution retrospective cross-sectional study design was conducted in patients with early laryngeal cancer (T1, T2 N0) registered with department of radiation oncology of a tertiary care centre of the central part of the state. The analysis was done in 28 patients who received 52.5 Gy in 15 fractions from June 2015 to December 2019. Protocol was based on Christie and RMH experience of hypofractionated radiation for early glottic cancer. The study got approval from Institutional Review Board with IRB No.90/2020

The study was based on Christie and Manchester study, calculated by P = 0.93, q = .07, d = .1.
Substituting formula

$$\frac{(Z\alpha)^2 pq}{d^2}$$

$$\frac{1.96\ x\ 1.96\ x.93\ x.07}{0.1\ x\ 0.1}$$

$$\frac{0.2500}{0.1} = 25$$

The data was collected from recorded data base of patients after getting their verbal consent. Even though sample size as per calculation is 25, we collected the data of all patients who received the particular radiation dosage schedule during the specified time period and this was used for data analysis.

Inclusion Criteria

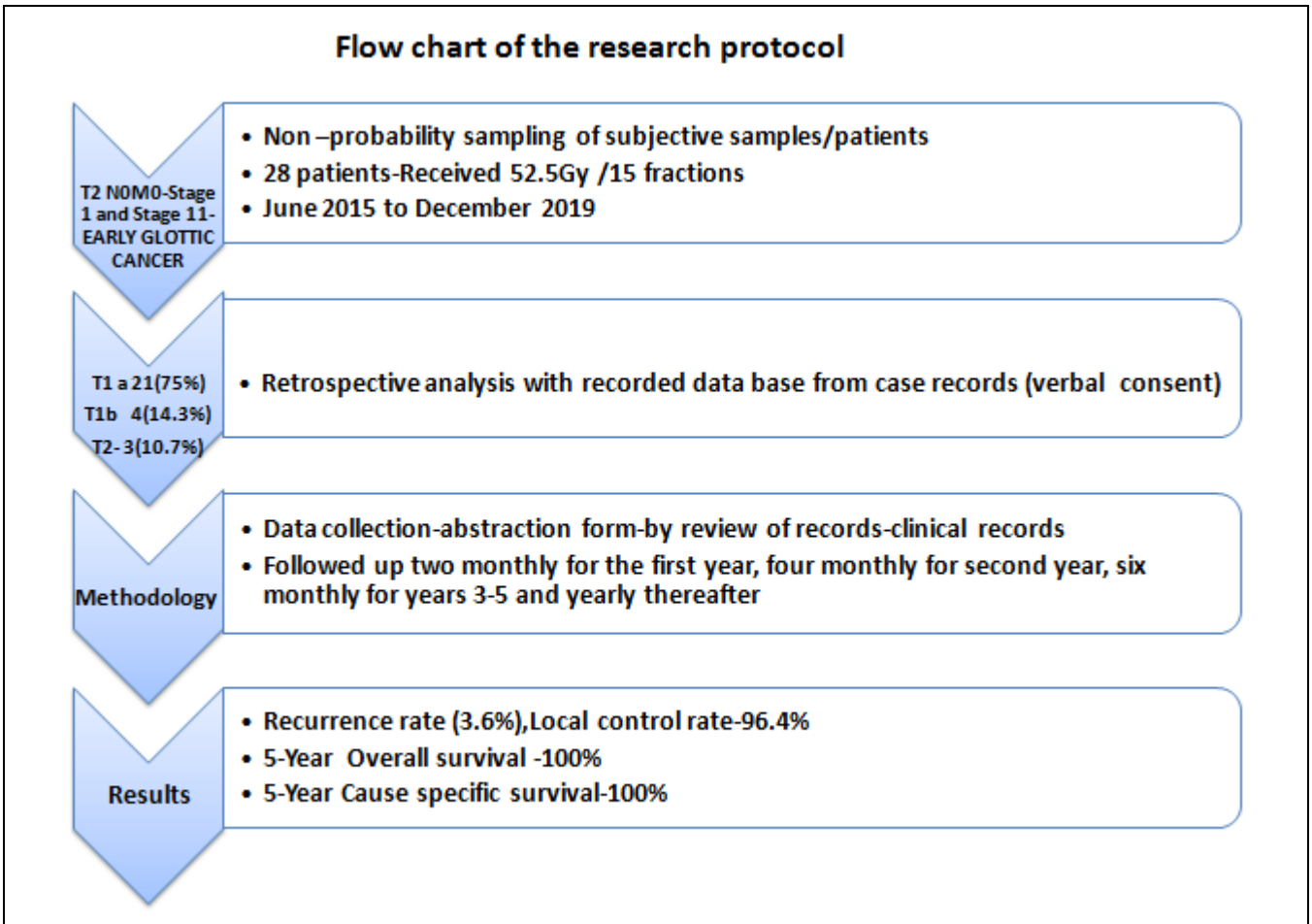
1. Patient's age above 18 years.
2. Eastern cooperative oncology group (ECOG) performance status 0 - 2.
3. Clinically stage I/II carcinoma glottis. (T1, T2N0)
4. Squamous cell carcinoma confirmed histologically by endoscopic biopsy.

Exclusion Criteria

1. Post-operative cases.
2. Pregnant patients
3. Eastern co-operative oncology group performance score > 3

Radiotherapy Details

Patients were treated with megavoltage photons in Linear accelerator (6 MV) or Theratron (Co60) machine. Four patients (14.3 %) were treated in cobalt 60 by 2D planning and 24 patients (85.7 %) in CLINAC linear accelerator by 3D conformal radiotherapy. All patients were treated supine fitted with an immobilization thermoplastic shell.



Flow Chart of the Research Protocol

In 3-D conformal radiotherapy, Clinac linear accelerator, Varian Medical Systems, Palo Alto CA delivering 6 MV photons was used. Planning CT scan with 3 mm axial cuts were taken from the C1 vertebral body to the thoracic inlet, with fiducials meant for laser alignment of patient and reproducibility of treatment position. The CT cuts were then imported to and contoured in eclipse treatment planning system. The thickening/exophytic or infiltrative true vocal fold mass of unilateral or bilateral vocal cords and anterior commissure were contoured as gross tumour volume (GTV) The clinical target volume (CTV) includes entire larynx starting from lower lower border of hyoid to lower border of cricoid. 5 mm margin was added to CTV to account for organ motion or setup error to derive the planning target volume (PTV). Volume of mucosa irradiated was considered from tip of epiglottis to inferior border of cricoid excluding external cartilage frame work. Mean dose received by this volume was recorded as mean laryngeal dose. The recommendation to reduce the risk of laryngeal oedema was to keep V50 Gy less than or equal to 27 % and mean laryngeal dose below 44 Gy. Voice quality was dependent on how far larynx and supra laryngeal structures were affected. In early laryngeal cancer, indirect effect by reduction in salivary function or direct effect on surrounding soft tissues and intrinsic musculature would be minimal. Hence, limiting mean dose of uninvolved larynx to 40 - 45 Gy and maximum dose to less than 63 - 66 Gy, based on tumour extent was tried. Respecting all the above issues, 3D conformal planning was done by geometric field shaping with multi-leaf collimator (MLCs), modulating field weight and dose normalization to improve target coverage. Plan was evaluated with dose distribution analysis and verified by comparison of portal image with digitally reconstructed radiograph (DRR) and treatment was then executed. The field size ranged from 5 X 5 cm to 8 X 9 cm, depending on length of neck and T stage of the tumour.

In Co 60 teletherapy, conventional 2-field technique with 5 X 5 or 6 x 6 wedged parallel opposed lateral fields were used with or without wax bolus of 0.5 cm thickness. Superior border was at the top of thyroid notch and inferior border at the bottom of cricoid cartilage. Anteriorly, sufficient flash (1 cm) was allowed to account for neck movements. Anterior edge of vertebral body was the posterior limit.

Regular follow up was advised every two months for the first year, every four months for second year, every six months for 3 - 5 years and yearly thereafter. Complete head and neck examination including mirror and fiberoptic were done at each visit. Imaging options were advised as and when needed. Thyroid stimulating hormone (TSH) every six monthly was advised.

Statistical Analysis

Local control, overall survival and cause specific survival were the endpoints analysed. Overall survival included death from any cause. Cause specific survival was the deaths reported due to this disease or deaths due to any cause within three months of start of radiotherapy. Survival curves were calculated using Kaplan Meier estimates. Pearson-chi square P value was used to find the test of significance.

RESULTS

The median age was 61 years. All patients were males 28 (100 %). The median follow-up period was 23.8 months. 92.9 % were smokers and 23 patients (82.1 %) used alcohol. 21 patients (75 %) were T1a, four were T1b (14.3 %) and three (10.7 %) were of T2 substage. Thirteen patients (46.4 %) had anterior commissure involvement and sixteen (57.1 %) had well differentiated tumours.

Median Age	61 Years	No.	%
Gender	Males	28	100%
	Females	0	0%
ECOG performance status	1	27	96.4%
	2	1	3.6%
Smoking	Yes	26	92.9%
	No	2	7.1%
Alcohol	Yes	23	82.1%
	No	5	17.9%
Benign laryngeal lesion	Yes	1	3.6%
	No	27	96.4%
Pre-treatment haemoglobin	Less than 13 g/dl	25	89.3%
	More than 13 g/dl	3	10.7%
Sub stage	T1a	21	75%
	T1b	4	14.3%
	T2	3	10.7%
Bulk of tumour	Small surface lesions	19	67.9%
	Bulky tumour	9	32.1%
Vocal cord involvement	Unilateral	24	85.7%
	Bilateral	4	14.3%
Anterior commissure involvement	Yes	13	46.4%
	No	15	53.6%
Histology	Well differentiated	16	57.1%
	Moderately differentiated	9	32.1%
	Carcinoma in situ with Foci of invasion	3	10.7%

Table. 1. Patient and Tumour Characteristics

Local control of the three-weekly schedule for early glottic cancer was 96.4 % with one recurrence (3.6 %). Recurrence was noted in one who continued smoking and alcoholism even after treatment completion. Acute coronary syndrome (ACS) with non-ST-segment elevation myocardial infarction (NSTEMI) was the cardiac complication reported in recurrent case. Local controls were T1a – 100 %, T1b – 100 % and T2 - 96.4 %.

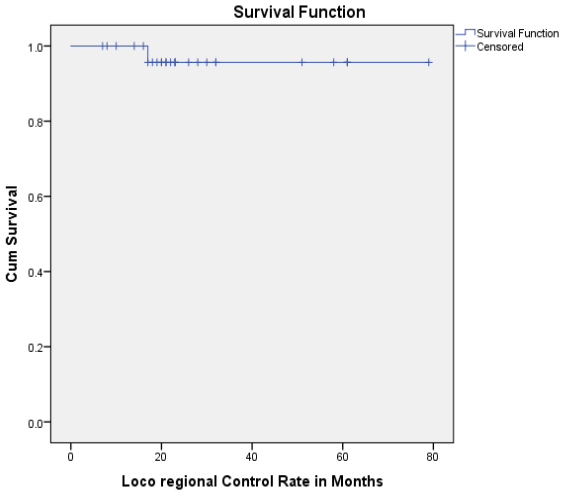


Figure 1. Local Control Rates in Months

Thirteen of the study participants (46.4 %) had anterior commissure involvement (AC). There was no significant association of anterior commissure involvement and local control (P = 0.408, chi square value = 3.982).

Factors	N (%)	P Value
Field Size		
< 6 x 6	2 (7.1 %)	P = 0.812, chi square value = 10.962
➢ 6 x 6	26 (92.9 %)	
Anterior Commissure Involvement		
Yes	13 (46.4 %)	P = 0.408, chi square value = 3.982
No	15 (53.6 %)	
Pre-treatment Haemoglobin		
< 13 mg/dl	13 (46.4 %)	P = 0.480, chi square value = 3.484
➢ 13 mg/dl	15 (53.6 %)	
Beam Energy		
2 MV	4 (14.3 %)	P = 0.098, chi square value = 7.840
6 MV	24 (85.7 %)	
Overall Treatment Time		
Up to 22 days	2 (7.1 %)	P = 0.747, chi square value = 1.938
25 - 30 days	26 (92.9 %)	

Table 2. Association of These Factors on Local Control

Local control in those with AC involvement was 100 % compared to 93.3 % when AC was not involved.

The other aim was to determine the impact of field size, anterior commissural involvement, beam energy and pre-treatment haemoglobin on outcome. There was no significant association of the above-mentioned factors on local control, overall survival and cause specific survival. There was no significant association of laryngeal oedema with mean laryngeal dose (Table 3) or volume of mucosal irradiation. (Table 4)

Laryngeal Oedema (%)	Mean Laryngeal Dose (Gy)	P Value
Nil (78.5 %)	53.3468	0.513
Garde 1 (17.9 %)	53.3357	
Grade 3 (3.6 %)	52.5000	
Total	**53.3137**	

Table 3. Association between Laryngeal Oedema and Mean Laryngeal Dose

There was no significant association between laryngeal oedema and mean laryngeal dose. Since the P value 0.513 is greater than 0.05.

Laryngeal Oedema (%)	Volume of Mucosal Irradiation (cm 3)	P Value
Nil (78.5 %)	50.6	0.356
Garde 1(17.9 %)	38.34	
Grade 3(3.6 %)	65.9	
Total		

Table 4. Association between Laryngeal Oedema and Volume of Mucosal Irradiation

There was no significant association between laryngeal oedema and volume of mucosal irradiation. Since the P value 0.356 is greater than 0.05

Complications	Frequency	Percentage
Radiation Dermatitis		
Nil	22	78.6 %
Grade 1	1	3.6 %
Grade 2	1	3.6 %
Grade 3	4	14.3 %
Laryngeal Oedema		
Nil	22	78.5 %
Grade 1	5	17.9 %
Grade 3	1	3.6 %
Voice Quality		
Good quality	24	85.7 %
Hoarseness	4	14.3 %
Thyroid Function Tests		
Normal	27	96.4 %
Altered	1	3.6 %
Cardiac Complication		
Nil	27	96.4 %
NSTEMI	1	3.6 %
Second Primary		
Nil	28	100 %

Table 5. Treatment Complications in the Study Period.

Organ preservation rate was 100 %. One patient recurred after sixteen months and was eligible for salvage surgery. He refused surgery, alive and is on palliative chemotherapy. There were no deaths among the study participants during

the median follow up period of 23.8 months. Overall survival and cause specific survival was 100 %.

The acute complication during treatment was acute radiation dermatitis scored according to common terminology criteria for adverse events (CTCAE) ver. 4.0. Grade 1 and 2 dermatitis was reported in one patient (3.6 %) each and Grade 3 in 4 participants (14.3 %).

Chronic treatment complications included laryngeal oedema (28.6 %), altered thyroid function test (3.6 %) and cardiac complication (3.6 %) and hoarseness in 4 (14.3 %). Grade 1(25 %) and Grade 3 (3.6 %) laryngeal oedema were reported in the median follow-up period of 23.8 months.

DISCUSSION

The 3-week hypofractionated radiotherapy schedule tried was based on the radiotherapy schedule practised in Royal Marsden and Christie hospitals, England on T1glottic cancers.[10] A randomized control trial (RCT) comparing conventional fraction and hypofractionation schedules for T2 glottic cancers done at Manchester, U. K by Dixon et al. Cetinayak[11,12] also supports the schedule.

The five-year local control rates were T1 glottic cancer 100 %, T1b - 100 % and T2 - 96.4 %. Local control rates for T1 glottic cancer of RMH & Christie Hospital was between 80 – 95 % with radiotherapy[10] and increased to 90 – 100 % with surgical salvage.[13,14] The 5-year local control rates reported by Dixon et al. in the RCT were 82 % for T2 glottic cancer in Christie Hospital, Manchester. Five year local control rates of 55 Gy in 20 fractions in St. John's Hospital, UK was 85.6 %, with T1 a - 91.8 %, T1b - 81.6 % and T2 - 80.9 %.[15] Tokai study group for therapeutic radiology and oncology (TOSTRO) in Tokai District Japan tried 63 Gy in 28 fractions with a local control rate of 86.5 % for T1 a and 83.6 % for T1b.[16] Local control in AC involvement was 100 % compared to 93.3 % with uninvolved AC. In RMH study by Gowda et al. local control was 94 % without AC involvement and 89 % with AC involvement.[10] Dixon et al. reported that T2 stage and anterior commissure involvement determined the prognosis for local control.[16]Involvement of AC on local control was controversial[17] In the 12 year retrospective review in 433 patients of T1 glottic cancer treated with radical radiation, Tong et al. stated that the negative impact of anterior commissure involvement on local control could be overcomed by increasing fraction size to more than 2 Gy. In multivariate analysis of local control and survival by Nomura T et al. age, T stage, size and subglottic extension were also identified as significant factors.[18, 16, 19]

The overall treatment time (OTT), fraction size, beam energy and biological effective dose (BED) were the treatment related parameters which influenced the outcome.[7, 8,20,17,21,22] Yamazaki et al. had clearly indicated that reduced OTT without dose reduction achieved by high fraction size can counteract accelerated repopulation and improve local control. The corrected BED calculation also utilized OTT with assumed lag period T_{lag} as 28 days for a burst of accelerated repopulation of tumour clonogenic cells and 0.6 as the rate of dosage loss in 2 Gy fractions.[22]

Biologically effective dose = $D(1+d/\alpha/\beta)-(OTT-L)\times T$(D = total dose, d = dose per fraction, OTT = overall treatment time, L = time lag, T= time factor, α/β = 10),calculated with time lag of 25 days and time factor of 1 to make BED values for local control of two regimes simlilar[22]

The radiation dose of 52.5 Gy in 15 fractions has BED of 70.9 Gy and EQD2 (equivalent dose in 2 Gy per fraction) of 59.1 Gy for tumour and BED of 113.8 Gy and EQD2 of 68.2 Gy for late reacting normal tissues. But for conventional schedule of 70 Gy in 35 fractions, BED for tumour is 84 Gy and EQD2 is 70 Gy and BED of 116.7 Gy and EQD2 70 Gy for late responding tissues. EQD2 received by the tumour in 15 days was 59.1 Gy in hypofractionated schedule and 30 Gy in conventional fractionation. EQD2 received by late responding tissues were 68.2 Gy for hypofractionated and 70 Gy for conventional explaining the good local control and decreased late toxicity. All the study participants had completed treatment in less than thirty days giving an added benefit. Extending the overall treatment time (OTT) was found to adversely influence local control, as demonstrated by Fein DA.[8,11,21,23] Le QT et al. established T2 lesions treated with OTT of < 43 days was associated with five-year local control of 100 % and 84 % with OTT of > 43 days.[8] Rudoltz et al. in their study reported the same result with disease-specific survival 97 % for treatment completed < 54 days and 80 % for > 55 days (P = 0.02).[24]

DAHANCA trial[25] explained the importance of accelerated regimes[9,26,27,15,16] in reducing risk recurrence in T1-T2 glottic cancers. Benefit of acceleration was noticed in well and moderately differentiated tumours that have cells with adequate and pronounced functional behaviour to respond to the radiation trauma. Well-differentiated squamous cell carcinoma has high labelling indexes (LI) and shorter potential doubling times (up to five days) bearing a greater propensity for accelerated repopulation. T1 glottic cancers are mostly well or moderately differentiated, slow growing and may contain a low proportion of dividing cells with a relatively low alpha-beta ratio. Harmful effects of larger doses/day used in accelerated regimes can be compensated for by delivering a lower total dose. The gain made in reducing the overall time compensates for the small reduction in total dose administered.[25,28,29]

The influence of beam energy on local control was demonstrated by Sombeck et al. and Lee et al.[30,31] Co 60 and 4 MV photons were considered optimal beam energies with better 5-year local control than 8 or 10 MV photons. Secondary electrons produced by high photon energies have to travel a longer distance to attain an electronic equilibrium. Anterior commissure is only 1 cm beneath the skin of the neck. But build up zone of high energy photons are located at a depth compared to Co 60 which is located 0.5 cm below skin surface. Inadequate build-up of electrons on the surface of air cavity located in the interior of larynx also contribute to under dosing of these regions. The subtle build up/build down dose changes close to the interfaces leading to considerable inaccuracies in these regions are more pronounced at higher energies. Absorbed dose at anterior commissure may be decreased by 12 % with 6-MV photons and 18 % with 10 MV photons on comparison with Co 60. In our study, the results of local control were similar for Co 60 and 6 MV photons. The number with Co 60 was inadequate to derive conclusive evidence regarding association between beam energy and local control outcomes. Bolus was used for build-up in patients treated with 6 MV photons. Lee et al. had

concluded that 6 MV photons seem to achieve similar local control as that of lower energy photons.[30]

Laryngeal oedema was correlated to mean laryngeal dose and volume of mucosal irradiation. Michael. T. Milano et al.[32] had reported the dose volume data of larynx. The one-year rate of laryngeal oedema with grade and mean laryngeal dose were as follows: Grade ≥ 2 oedema (%) – 20 % with MLD 43.5 Gy and V50 < 27 %, 45 % with MLD 44 - 57 Gy and V50 > 27 % - < 94 %, > 80 % with MLD > 57 Gy and V50 > 94 %.

Table 3. shows 78.5 % of the study participants had no laryngeal oedema with a mean laryngeal dose of 53Gy, Grade 1 in 17.9 % with MLD of 53 Gy and grade 3 in 3.6 % with MLD of 52.5 Gy. Grade 3 oedema underwent tracheotomy with volume of mucosal irradiation 65.9 cm^3 and MLD 52.5 Gy. No significant association between laryngeal oedema and mean laryngeal dose was present (P value 0.513).

The laryngeal oedema was scored according to radiation therapy oncology group scale as 0 - no oedema; 1 - slight oedema; 2 - moderate oedema; 3 - severe oedema and 4 - necrosis. Mendenhall et al. reported moderate and severe complications in fraction size of greater than 2.25 Gy.[4,6,33,22] Yamazaki found that rate of laryngeal oedema was not different in two groups.[7]

The risk of radiation dermatitis is dependent on total dose, fraction size and dose volume to surfaces. In low energy techniques, it was observed that Grade 1 - erythema after doses ≥ 2 Gy, Grade 2 - dry desquamation after doses of 12 - 20 Gy, Grade 3 - moist desquamation doses >20 Gy and Grade 4 - necrosis at doses ≥ 35 Gy.[34] Grade 1 and 2 dermatitis was reported in one patient (3.6 %) each and Grade 3 in 4 participants (14.3 %).

Rancati et al.[35] suggested limiting 40 - 45 Gy as the mean non-involved laryngeal dose and less than 63 - 66 Gy as the maximum laryngeal dose, depending on possible tumour extent. In our study group, 85.7 % participants had good voice quality and 14.3 % had hoarseness similar to that of three weeks radiotherapy schedule of Christie Hospital and Royal Marsden for T1 glottic cancer.[10]

There were no second primary tumours reported with our schedule. The series[10] reported from literature had quoted a 5-year actuarial incidence of 9.3 % and an annual risk of 3 – 5 %.

Swisher-McClure et al.[36] observed that the cumulative incidence of fatal CVA at 15 years was 2.8 % with external beam radiation therapy (EBRT) and 1.5 % with surgery with an adjusted hazard ratio of 1.75. No cerebrovascular accident (CVA) was reported in our study participants.

CONCLUSIONS

Early glottic cancer (T1, T2) is treated either with radiotherapy or surgery. Hypofractionated radiotherapy schedule of 52.5 Gy in 15 fractions practiced in our centre has 96.4 % local control, 100 % overall survival, and 100 % cause specific survival comparable with the similar series quoted in the literature. Well/moderately differentiated early squamous cell carcinomas of glottis derived maximum advantage with preservation of voice quality, good local control and excellent survival. There was no significant association of field size, anterior commissure involvement, beam energy and volume of mucosal radiation on immediate and late treatment outcomes.

The schedule offers convenient shorter fractionation regime with large fraction size, logistic benefits and shorter overall treatment time. Hence, the schedule seems attractive in resource limited centers with long wait for radiation.

Limitations of the Study

Majority of the patients belonged to T1a sub stage 75 %. T1b and T2 sub stages were only 14.7 % and 10.7 % and so the result of the study was a reflection of results for T1a and this cannot be extrapolated equally for other sub stages. Hence, a prospective study with similar number of study participants for all sub stages would be required to derive an acceptable conclusion for other sub stages.

Ultimate local control would have been better provided the patient who recurred had surgical salvage.

The current report was a retrospective single institutional study which may be subjected to biases and it lacks prospective measurement of voice quality.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jemds.com.

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