

Comparison of Two Different Radiation Fractionation Schedules in Early Stage Carcinoma Larynx

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ABSTRACT

Introduction: Carcinoma of larynx which is linked directly with smoking is emerging a very big public health problem. In our study, we have treated cases of early glottic carcinoma by two different dose fractionation schedules in relation to overall treatment time and have tried to assess the response of two different fractionation schedules.

Material and Methods: This is an analysis of 29 patients with invasive, previously untreated T₁ and T₂ squamous cell carcinoma of true vocal cord that were treated by radical radiation therapy. All patients were treated with a continuous course of radiation therapy with once daily fractionation. All the patients were treated 5 days a week from Monday to Friday. The fractionation regime was either:

- 62.5Gy/25fractions/5 weeks@2.5Gy/fraction (Regimen-1)
 - 70 Gy/35 fractions/7 weeks@2 Gy/fraction (Regimen-2)
- Regimen-1 included 15/29 patients (51.72%) and Regimen-2 included 14/29 patients (48.27%).

Results: There was no significant difference in terms of loco-regional control rate, acute and late radiation toxicities in both groups. Voice quality during and after radiation was comparable in both arms.

Conclusion: Use of high dose per fraction schedule with shorter duration of treatment results in comparable local control as well as quality of voice to the protracted course of radiotherapy without increase in treatment related toxicities. Shorter overall treatment time can be of great advantage in terms of time, cost, comfort and acceptability by the patients.

Keywords: Carcinoma Larynx, Radiation Therapy, Early Glottic Cancer, Radiation Fractionation Schedule, Accelerated Hypofractionated Radiation.

INTRODUCTION

Carcinoma of larynx, along with carcinoma of the oral cavity, is the most common primary head and neck malignancy. Laryngeal tumors represent 2% of total cancer risk.¹ Laryngeal cancers is important since it affects organ of voice, and disease as well as treatment can alter the functional aspects of the voice. Carcinoma of larynx is strongly related to smoking.² Alcohol has synergistic effect if consumed along with smoking. On an average world statistics quote the incidence of laryngeal carcinoma as 4-5 per lac of population. In India, the population-based registry estimates an annual incidence of nearly 25000 new cases of laryngeal carcinomas. The incidence of laryngeal cancers in India is 8.5 per lac in males and constitutes 7.4% of all cancers in men. The male: female ratio is 4:1. In Indian subcontinent, Supraglottic carcinomas are twice more common compared to glottic carcinomas. Globally the ratio of glottic to supraglottic carcinoma is approximately 3:1.¹ Laryngeal carcinoma is predominantly a male disease. The male: female ratio is 12:1

for glottic cancer and 4:1 for supraglottic cancers. Our institution records approximately 150 cases of carcinoma larynx in a year. More than two-third of these cases are supraglottic carcinomas. It has been estimated that, 70 to 80% of the supraglottic carcinoma present in stage III and IV. In treatment of vocal cord carcinoma, goal is to maximize control rates with voice preservation using radiation therapy and surgery, either alone or in combination. Early stage carcinomas can be treated by radical radiation therapy or in selected cases, by partial Laryngectomy or endoscopic CO₂ LASER cordectomy. The advance stage disease is treated by combined modality in the form of total Laryngectomy and neck dissection with or without adjuvant radiotherapy or by radiation therapy and concomitant chemotherapy.³⁻⁴

In our study, we have treated cases of early glottic carcinoma by two different dose fractionation schedules i.e. (62.5 Gy in 25 fractions at rate of 2.5 Gy per fraction and 70 Gy in 35 fractions at rate of 2Gy per fraction) in relation to overall treatment time. Use of high dose per fraction schedule with shorter duration of treatment results in comparable local control as well as quality of voice to the protracted course of radiotherapy without increase in treatment related toxicities. Our study was designed to:

1. To assess the response of two different fractionation schedules i.e. (62.5 Gy in 25 fractions at rate of 2.5 Gy per fraction and 70 Gy in 35 fractions at rate of 2Gy per fraction).
2. To evaluate, loco regional control in relation to total dose, fractionation schedule, dose per fraction and overall treatment time.
3. To determine certain tumor related parameters that may influence local control.
4. To analyze early and late toxicities of radiation therapy.
5. To examine the functional quality of voice following radiation therapy and influence of various treatment parameters.

MATERIAL AND METHODS

Patient Characteristics

This is an analysis of 29 patients with invasive, previously

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untreated T₁ and T₂ squamous cell carcinoma of true vocal cord that were treated by radical radiation therapy. All patients were treated with curative intent with a continuous course of radiation therapy with Telecobalt. All the patients are alive and are on regular follow up.

Staging: Pre-treatment evaluation included history, physical examination, chest X-ray, complete blood count, fibre optic direct laryngoscopy with biopsy and diagnostic Computed Tomography (CT) scan of neck.

After meticulous work up, the patients were staged. Patients with T₁N₀M₀ (stage I) and T₂N₀M₀ (Stage II) were included in our study. The patient's agreement and a written consent to participate in the study were taken. All the cases had to undergo an approval of the tumor board.

Inclusion Criteria

1. Good Karnofsky performance scale (>70%)
2. T₁N₀M₀ and T₂N₀M₀ disease
3. Biopsy proven carcinoma
4. Patient willing to be enrolled in study
5. Willing for long-term follow up

Treatment Procedure

All patients received continuous course of radiation therapy with once daily fractionation. All the patients were treated 5 days a week from Monday to Friday.

Dose and Fractionation

The fractionation regime was either:

- 62.5Gy/25fractions/5 weeks@2.5Gy/fraction (Regimen-1)
- 70 Gy/35 fractions/7 weeks@2 Gy/fraction (Regimen-2)

It was 2.5Gy/fraction (Regimen-1) in 15/29 patients (51.72%) and 2Gy/fraction (Regimen-2) in 14/29 patients (48.27%).

Monitoring of the patients on radiotherapy

The patient acute morbidities were charted on RTOG (Radiation therapy Oncology group) morbidity criteria chart. The late toxicity was assessed by LENT-SOMA score. At least 5 parameters were noted and grading (Grade 0 to IV) was done every week. The parameters were related to Skin, Mucous membrane, Salivary gland, Pharynx and Oesophagus, and Larynx.

All the patients completed their planned treatment in stipulated time and none had to discontinue their treatment due to acute toxicity.

Follow up after treatment: Patient were followed up regularly at increasing intervals and were evaluated for:

- Loco Regional Control
- Quality of Voice
- Late toxicity of radiation therapy

Voice Assessment

Voice assessment after radiation therapy was done by:

- A. Voice quality
- B. Vocal function
- C. Vocal performance

To assess the vocal performance, the patients were given a questionnaire, which they had to answer at first, second and third follow up post treatment. Our questionnaire was based on pattern of University Medical Centre, Amsterdam, Neth-

erlands. The questions were:

1. Do you have to strain to produce voice?
2. Do you have problem in shouting?
3. Do you have problem in making a telephone call due to voice?
4. Do you encounter problems holding conversation due to your voice?
5. Does your voice change from day to day?

Scoring as follows:

- 0 – Yes
- 1 – Occasional
- 2 – No

Score Vocal Performance

- 0 to 3 - Impaired
- 4 to 6 - Satisfactory
- 7 to 10 - Good

Voice Quality assessment was done as follows.

1. Unpleasant or pleasant
2. Breathy or not breathy
3. Dull or clear
4. high or low
5. Shrill or deep

Score 1 - Unfavourable answer

Score 2 - Favourable answer.

The minimum and maximum score was 5 and 10 respectively. The higher the score, better the voice quality.

Score Voice Quality

- 5 to 7 - Normal
- 8 to 10 - Deviant

STATISTICAL ANALYSIS

Analysis was done using statistical tool SPSS 11.0. Two-tailed corrected chi-square test and unpaired *t*-test were used for p value calculation. The results were studied on an intention-to-treat basis.

RESULTS

Twenty nine patients of early glottic carcinoma were found eligible for radical radiation therapy. All the patients successfully completed the treatment within the stipulated time and are on regular follow up. The overall treatment time ranged from 34 to 37 days for Regimen-1, while it was between 48 days to 53 days in Regimen-2. The Patient and Tumor related characteristics are detailed in Table 1.

Outcome

Follow up period of patients ranged from 6 months to 2 years with a median follow up of 18 months.

The local control rate with radical radiation therapy at 18 months was 90% as 26 out of 29 patients had complete response to radical radiation therapy. Thus, the local control rate in Regimen 1 was 93 % (14/15 patients had local control). The locoregional control rate in Regimen 2 was 85 % (12 /14 patients had local control).

These 3 patients who had local failure underwent total laryngectomy. None of the patients developed recurrence after total laryngectomy, neither at the primary site nor in the neck nodes. All the patients are on regular follow up and are controlled for the disease.

The tumor variables tested for an association with local control included-

1. T₁ and T₂ stage
2. Extensions to Supraglottic and Subglottis
3. Impaired vocal cord mobility
4. Anterior commissure involvement
5. Field size
6. Regimen 1 and 2

1. T₁ and T₂ stage

The local control rate for T₁ lesion was 92% and for T₂ lesion was 88%. (p value=0.05).

2. Supraglottic and Subglottic extension

Of the 17 patients with T₂ stage, 6 patients (35%) had supraglottic spread. Out of these 6 patients, one patient had failure (1/6=16%). The subglottic extension was present in only 1 patient with the involvement of whole cord and this patient also patient developed local failure (p value < 0.01).

Loco regional control in patients with localized disease was 95% and it was 71% for disease with extension beyond glottis.

3. Impaired vocal cord mobility

Out of 17 patients of T₂ tumors, 11 patients (65%) had impaired vocal cord mobility. Of these 11 patients, 3 patients had supraglottic extension as well as impaired mobility of vocal cord. The other 8 patients had localized disease with impaired mobility. One of the patients with supraglottic extension as well as impaired mobility developed local failure. The local control rate with impaired mobility and normal mobility was 82% and 94% respectively (p Value = 0.04).

4. Anterior commissure involvement:

In our study, 14 out of 29 patients had anterior commissure involvement. The local control rate with and without anterior commissure involvement is 86% and 93% respectively (p Value = 0.5).

5. Field Size

Radiation field did not influence local control. The 2 year local control rate treated with:

- 36 Cm² - 94 %
- 42Cm² - 86 %
- 49 Cm² - 86 %

Radiation Toxicities

Comparison of acute toxicities of Regimen 1 and 2 is detailed in Table 2.

Difference in the acute and late toxicities in both the arms was statistically non-significant. High dose per fraction was well tolerated by the patients although the toxicity was marginally, but yet it was very much acceptable, as none of the patients had to discontinue their treatment due to acute morbidity.

Majority of the patients had Grade 1 late toxicity. No severe late complication was observed in either of the Regimens. None of the patients developed radio necrosis or second primary in our set up. However, long term follow up is warranted to come to a definite conclusion.

Voice quality during and after treatment

Majority of the patients showed improvement in voice in

Parameter	T ₁ (n=12)	T ₂ (n=17)	Total (n=29)
1. Gender			
Male	11	16	27 (93%)
Female	1	1	2 (7%)
2.Age(In years)			
<59	6	7	13 (45%)
≥59	6	10	16 (55%)
3. Smoking	11	14	25 (86%)
4. Alcohol	4	2	6 (20%)
Parameters	Number of patients		
	T₁(n=12)	T₂(n=17)	Total (n=29)
1. Site of Lesion:			
Anterior 2/3 only	1	2	3(10%)
Cord + AC	4	10	14(49%)
Mid cord	5	4	9(31%)
Whole cord	2	1	3(10%)
2. Disease extent	0	6	6(21%)
Supraglottic			
Subglottic	0	1	1(3%)
3. Mobility of the cord	All had mobile vocal cord	11 patients had impaired mobility	11(38%)
4. Growth type			
Exophytic	10	13	23(79%)
Infiltrative	2	4	6(21%)
5. Biopsy: S.C.C			
Grade: I	9	12	21(72%)
II	2	2	4(14%)
III	1	3	4(14%)
AC – Anterior Commissure, S.C.C – Squamous Cell Carcinoma, n - Number of patients			

Table-1: Patient and Tumor characteristics

	Regimen I (n=15)	Regimen 2 (n=14)	P Value
Skin			
Grade I	11(73%)	11(78%)	NS
Grade II	4(26%)	3(21%)	NS
Grade III	0(0%)	0(0%)	NS
Mucous membrane			
Grade I	3(20%)	2(14%)	NS
Grade II	10(66%)	10(71%)	NS
Grade III	2(13%)	2(14%)	NS
Pharyngitis			
Grade I	11(73%)	4(28%)	<0.05
Grade II	3(20%)	10(71%)	<0.05
Grade III	1(7%)	0(0%)	NS
Voice			
Grade I	4(26%)	0(0%)	<0.05
Grade II	8(53%)	9(64%)	NS
Grade III	3(20%)	5(36%)	NS
Cough			
Grade I	10(66%)	11(78%)	NS
Grade II	5(33%)	3(21%)	NS
Grade III	0(0%)	0(0%)	NS
NS – Non Significant			

Table-2: Acute Toxicity Grading in Regimen I and II

first 2 to 3 weeks after commencing of radiation therapy. In general, the hoarseness reappeared in subsequent weeks. The voice started to improve again approximately 2 to 3 weeks after completion of Radiotherapy and voice reached a plateau in 2 to 3 months. The improvement of voice was almost comparable in both groups.

Results of Voice Quality

Majority (86%) of the patients on follow up had normal voice quality.

The 4/29(14%) patients did not had a satisfactory improvement in their voice. Three of the patients among these had local treatment failure. Thus, poor voice or deterioration of voice can be the first sign of local failure or recurrence of laryngeal cancers.

DISCUSSION

Radiation therapy for early glottic cancers offers an excellent probability of cure. The dual objective of treatment: controlling the malignant tumor and preserving a functionally useful voice is best optimized by the use of radical radiotherapy in early glottic cancers. Although Surgery can undoubtedly offer good results, it is best reserved in the event of radiation failures, with patients still given a second chance of cure.⁵⁻⁶ Comparative data of incidence, sex distribution and site wise distribution of carcinoma larynx is detailed in Table 3.

Management of Early Glottic lesions

Radical Radiation therapy is standard treatment option for stage T₁-T₂ glottic cancers. Staplers *et al*, observed that while radiotherapeutic techniques and schedules varied in different centres, the 5 year overall Survival rates only varied from 85-95% for T₁ lesions and 80-90% for T₂ lesions. The disease free survival at 5 years averaged at a mean of 84% for T₁ and 70% for T₂ lesions.

In our study, the local control and overall local control including Surgical Salvage at 2 years was 92% and 100% for T₁ whereas it was 88% and 100% for T₂ lesions.

Factors Influencing local control

A. Stage: - Earlier the stage, the better is local control and overall survival. Mendenhall *et al*,⁷ in 1988 reported a local control rate of 93% and 75% for T₁ and T₂ respectively.

Our Study Results: (According to stage)

The local control rate of our study at 2 years follow up was 92% for T₁ and 88% for T₂ lesions. The two years overall local control with surgical salvage and survival was 100%.

B. Anterior Commissure involvement

Some authors including Mantravadi *et al*, and Kirschner *et al*, reported decreased local control rates when there was anterior commissure extension and the primary lesion was treated with Radiotherapy alone.⁸ Fein *et al*, found no significant relationship between the likelihood of local control and tumor involvement of anterior commissure. In a study at Tata Memorial Hospital by Dinshaw *et al*, anterior commissure did not adversely affect the local control: 82% as compared to 85 % with and without involvement of anterior commissure (p value not significant)

In our study, local control was not significantly influenced by the presence of anterior commissure involvement. The local control rate with and without involvement of anterior commissure was 86% and 93% respectively. (p value =0.5).

C. Impaired Vocal Cord Mobility

Impaired mobility had been shown by various authors to result in increased local failures.⁵ Harwood and De Boer reported a 21% difference in 5 year survival and a 25% difference in local control depending on whether the cord was mobile or not.⁹⁻¹² Dinshaw *et al*, reported that impaired cord mobility did not adversely affect the local control rates at ten

Parameters	Globally	India	Our Centre
1. Incidence(% of all cancers in Male)	2%	7.4%	6%
2. Male: Female	6:1	4:1	4:1
3. Site wise distribution (supraglottic: Glottic)	1:3	3:1	3.6:1
4. Histopathology	90% or more is squamous cell carcinoma	95% or more is squamous cell carcinoma	98% are squamous cell carcinoma others chondrosarcoma and Adenocarcinoma

Table-3: Comparative data of incidence, sex distribution and site wise distribution

Centres for Trial	No. of Patients		Local Control Rate (%)		Ultimate Local Control Rate (%)	
	T ₁	T ₂	T ₁	T ₂	T ₁	T ₂
Prince Margaret Hospital(Toronto) ²¹	333	244	86	69	-	-
MD Anderson Cancer Centre(Houston) ²²	332	275	89	74	98	94
Tata Memorial Hospital ²³	460	216	82	57	-	-
University of (San Francisco) ²⁴	183	42	80	52	97	90
University of Florida, Gainesville	184	120	93	75	97	94
University of Florida ³	171	108	93	75	58	74
Massachusetts General hospital ¹⁹	665	237	93	71	98	-
Klintonberg et al	129	94	90	74	75	38
University of Maryland(Baltimore)	86	34	92	88	99	94

Table-4: Control Rate of T₁ and T₂ Glottic Cancers treated at various Institutes with Radical Radiotherapy

years, having 75% control rates in comparison to the mobile vocal cord group with 58% (p Value=0.48). Murakami *et al*, reported no difference in the 5 years local control rate with impaired cord mobility. They reported local control rate of 76% and 75% with mobile and impaired vocal cord (p Value=0.8).

In our study, the local control rate for with and without impaired mobility of the vocal cord was 82% and 94% respectively (p value =0.2).

D. Subglottic Extension

The T₂ lesion with subglottic extension of glottic Carcinoma also has adverse prognostic outcome. Le *et al*,¹³ reported local control of 77% for lesions without subglottic extension compared with 58% for subglottic extension (p Value=0.55). Dinshaw *et al*, reported a local control rate of 64% with subglottic extension as compared to 77% without subglottic extension (pValue=0.71). However, Murakami *et al*, reported 5 year local control rate of 66% and 80% with and without involvement of subglottis respectively (p Value = 0.0001).

In our study, only 2 patients had subglottic extensions and both of them had local treatment failure (p value =0.001).

E. Dose, Fractionation Schedule and overall treatment time

Mendenhall *et al*,¹⁴ reported that for patients treated once daily, 5 days per week, fractionation schedules using dose >2 Gy per fraction are superior to those using 1.8 Gy per fraction. Million *et al*, reported a trend of improved local control rates in patients treated with higher dose per fractions and shorter over all treatment time.¹⁵⁻¹⁷ Harwood *et al*, and Karim *et al*, suggested that the dose response curve for local control of T₁ tumors is almost flat between 55-66 Gy and that increasing the dose will not results in any improvement.⁹⁻¹²

Wang and Efir reported 5 year local control rates of 95% for patients with T₁ laryngeal tumor whose OTT was 60 days or less versus 60% for patients whose treatment time was >60 days (P=0.0056).¹⁸⁻²⁰

Rudoltz *et al*, reported local control rates of 100% if treatment was completed within 42 days, 91% for 43-46 days, 74% for 45-50 days, 65% for 51-54 days and 50% for 55-56 days(P=0.0001).

Mendenhall *et al*, reported a local control rate of 100% when T1 tumor was treated with total dose of 61-67Gy in 2.25 Gy per fraction. In contrast, the local control rate was only 80% for patient treated with 2Gy to 2.2 Gy per fractions.³

Chatani and Nishiyama *et al*, from Japan, concluded that 2.25 Gy per fraction scheme with a shorter overall treatment time is superior to 2 Gy/fraction for local control of T₁ glottic carcinoma. (92% versus 77%, P=0.003).

In our study, the result was definitely better in Regimen-1, (62.5Gy in 25 fractions) in which local control rate was 93% as compared to 85% in Regimen-2 (70Gy in 35 fractions) (p Value=0.5).

Field Size

The importance of field size in the treatment of T₁ and T₂ glottic carcinoma remains controversial. Teshima and Chatani *et al*, reported field size has an influence in the local control after Radiotherapy. Loco regional control remains same

irrespective of field size as long as entire target is covered well. Chatani *et al*, reported 3 year recurrence free survival of 88% in a randomized study of 273 patients of T₁N₀M₀ tumors using field size of 5x5 cm or 6x6 cm field size and 80% local control rate with field size of more than 6 x 6 cm (p value significant). Fein *et al*, reported 2 years local control of 90% for field size of <36cm² as compared with 86% for >36cm²(p Value=0.001). Historically, University of Florida and the Massachusetts General hospital have used field size of less than or equal to 5x5 cm and they have reported an excellent local control rates with minimal complications.^{5,19} In our study large field size had an adverse effect. Local control rate for field size less than 36cm² was 94% while it was 86% for field size more than 36cm² (p value not significant).

Beam Energy

In our set up all the patients were treated by Telecobalt-60. However, early glottic carcinoma can also be treated by 4-6MV LINAC machine. Mendenhall *et al*,⁵ compared cobalt-60 with 6MV and found no significant difference in the dose received at any point along the vocal cords. Cobalt-60 was the beam of choice for Mendenhall *et al*,⁵ in their series.

CONCLUSION

Radical Radiotherapy is the standard of care for early carcinoma glottis. It is well tolerated by patients without any significant complications. Radiotherapy has major advantage in terms of preservation of natural voice, high local control rate and overall survival. In our study, use of high dose per fraction schedule with shorter duration of treatment results in comparable local control as well as quality of voice to the protracted course of radiotherapy without increase in treatment related toxicities. Shorter overall treatment time can be of great advantage in terms of time, cost, comfort and acceptability by the patients. Shorter treatment time reduces the burden in a busy department and also decreases the cost of treatment in relation to time and money. This form of treatment demands a stringent criterion of patient selection, and quality assurance in terms of target volume delineation, treatment technique, treatment planning, verification and execution.

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