



## PROSPECTIVE STUDY TO COMPARE CONVENTIONAL CHEMO RADIOTHERAPY WITH HYPOFRACTIONATED CHEMO RADIOTHERAPY IN LOCALLY ADVANCE CARCINOMA OF LARYNX

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### ABSTRACT

**Background:** Laryngeal cancers represent one-third of all head and neck cancers and maybe a significant source of morbidity and mortality. The laryngeal cancer occupies an important position amongst all head and neck cancers since it affects the voice organ, and the disease and treatment can alter the functional aspects of voice. Fractionated radiotherapy, in turn, may sensitize tumours to chemotherapy by inhibiting the repair of drug induced damage and by decreasing the size of the tumor mass, leading to improved blood supply and enhanced drug delivery. hypo fractionated schedule can be expected better because the shorter treatment time with same efficacy compared with slandered fractionation. **Material And Methodology:** Patients, having histo-pathologically proven squamous cell carcinoma of Larynx suitable for radiotherapy. All patients received chemo-radiotherapy of Arm A EBRT// 20#/300cGy per#/4 week With Inj. cisplatin 100mg/m<sup>2</sup> x 3 weekly. Arm B EBRT// 70 Gy / 35 #/200cGy per #/ 7 week /With Inj. cisplatin 100mg/m<sup>2</sup> x3 weekly. **Result:** Most cases belonged to stage IV advanced stages of disease. 65 patients were recruited over 18 months, randomize in Arm A (35) and in Arm B (30). Tumor response at 6 months CR 13(43.3%), 10(45.5%) PR 7(23.3), 2(9.1%) and SD 0(0), 3(13.6%) in arm A and Arm B respectively (p value 0.187). Death was in 3(10%) and 1(4.5%) patients and lost to follow up were 7(23.3%) and 6(27.3%) in Arm A and B. Overall survival(OS) at 2 months, At 6 months, At 1 year with Mean  $\pm$  SD in arm A was 100, 96.4  $\pm$  3.5, 71.8  $\pm$  11.1 and in Arm B was 95.8  $\pm$  4.1, 86.8  $\pm$  7.1, 65.1  $\pm$  19.5 respectively (p value 0.516). Disease free survival (DFS) at 6 months with Mean  $\pm$  SD in Arm A was 61.1  $\pm$  13 and in Arm B was 70.7  $\pm$  12.1 respectively (p value: 0.819). **Conclusion:** Hypo fractionated radiotherapy with concurrent cisplatin every 3 weeks is a reasonable alternative to the standard fractionated regimen with concurrent cisplatin offers advantages of decreased overall treatment time, better compliance, decreased hospital stay with comparable response rate and toxicity profile.

### KEYWORDS :

#### BACKGROUND

Head and neck squamous carcinoma is the sixth most common cancer worldwide, with 890,000 new cases and 450,000 deaths in 2018.<sup>1,2,3</sup> The incidence of HNSCC continues to rise and is anticipated to increase by 30% (that is, 1.08 million new cases annually) by 2030 (Global Cancer Observatory (GLOBOCAN)).

Laryngeal cancers represent one-third of all head and neck cancers and maybe a significant source of morbidity and mortality. The laryngeal cancer occupies an important position amongst all head and neck cancers since it affects the voice organ, and the disease and treatment can alter the functional aspects of voice.

In conventional fractionation 200 cGy per day 5 days a week which may not be appropriate for each and every situation considering the radiobiological parameters fractionation regimen can be altered for different tumours.

A rationale for combining chemotherapy and radiotherapy concomitantly in the treatment of locally advanced laryngeal cancer exists. Chemotherapy can sensitize tumors to radiotherapy by inhibiting tumor repopulation, preferentially killing hypoxic cells, inhibiting the repair of sub-lethal radiation damage, sterilising micro metastatic disease outside the radiation fields and decreasing the tumor mass, which leads to improved blood supply and reoxygenation. Fractionated radiotherapy, in turn, may sensitize tumours to chemotherapy by inhibiting the repair of drug induced damage and by decreasing the size of the tumor mass, leading to improved blood supply and enhanced drug delivery. hypofractionated schedule can be expected to win out over the SF or HF schedule, because the shorter OTT achieved with the hypofractionation scheme reduces the socio-economic burden for patients and radiotherapeutic institutions; patients benefit from the reduced costs and treatment time. This would enable radiotherapeutic institutions to maintain the mechanical and human resources required to meet the increasing demand for radiotherapy.

#### MATERIAL AND METHODOLOGY

Patients with non metastatic locally advanced Carcinoma Larynx reporting between January 2021 to August 2022 were evaluated and all necessary investigations were done and eligible patients were

randomly divided into two groups: This group comprised of patients randomly selected patients, having histo-pathologically proven squamous cell carcinoma of Larynx suitable for radiotherapy. All patients received chemo-radiotherapy of Arm A EBRT// 20#/300cGy per#/4 week With Inj. cisplatin 100mg/m<sup>2</sup> x 3 weekly. Arm B EBRT// 70 Gy / 35 #/200cGy per #/ 7 week /With Inj. cisplatin 100mg/m<sup>2</sup> x3 weekly.

#### ASSESSMENT DURING TREATMENT

From the commencement of treatment, all the patients included in the study were carefully and regularly assessed weekly during treatment for response and acute toxicities.

#### ASSESSMENT AFTER THE COMPLETION OF TREATMENT

All the patients were assessed 6 weeks after the completion of treatment, to detect acute complications like mucositis, skin reaction. Acute treatment related toxicity were graded using common terminology criteria for adverse events and late toxicity by RTOG criteria. The tumor response was assessed by using the( RECIST 1.1 )criteria. Radiological assessment for tumor was done when indicated. All the patients were followed up regularly on OPD basis for a period of at least six months, weekly for four weeks in first month and then monthly.

At every visit, each patient was clinically evaluated for local control of disease and treatment related complications. The patients were assessed for any evidence of distant metastasis during each follow up. At the end of 6 weeks post RT, laryngoscopy was done to assess the disease status and also CECT neck was done at that time. To evaluate the local disease control, local examination using inspection palpation was done at each follow up and response was assessed. On the suspicion of any local recurrence, biopsy was taken for histopathology and correlated clinically. To evaluate the distant metastasis detailed history pertaining to any symptoms was taken and general physical examination of patients was done. In case of suspicion, relevant investigations were done to rule out the presence of distant metastasis. The QOL was assessed at the beginning of treatment, on the day of completion of treatment and one month after completion of planned treatment using University of Washington QOL questionnaire. The results of the study regarding safety, tolerability, toxicity and response in all the groups were documented.

## RESULTS

The predominantly affected age group was between 41-70 table 1 and both the arm balanced in form stage and sex distribution. Males are more commonly affected than females. Most of the patients had addiction habits of bidi/cigarette smoking with increased frequency and duration. Most cases belonged to stage IV advanced stages of disease. 65 patients were recruited over 18 months, randomized in Arm A (35) and in Arm B (30). Out of which 5(14.3%) and 6(20%) patient in Arm A and Arm B respectively defaulted treatment, excluded from the study. Fifty four patients completed planned dose radiotherapy in both the arms with median treatment time of Less than six weeks in Arm A while in Arm B it was more than eight weeks (p value <0.001). All patients completed a median follow up between 6 to 18 months. Grade I, II and III skin reactions 27(90%), 2(6.7%), 1(3.3%) in Arm A, and 22(91.7%), 2(8.3%), 0(0%) in Arm B patients respectively. In mucosal reaction we noticed Grade I, II and III toxicity in was seen in 8(26.7%), 20(66.7%), 2(6.7%) in Arm A and 14(58.3%), 9(37.5%), 1(4.2%) in Arm B patients respectively (acute toxicity). No grade IV skin and mucosal toxicity noted in both the arms. Maximum mucositis range lies between grade II and grade III toxicity which was manageable. During treatment Ryles Tube dependency noticed in 6(20%) and 2(8.3%) in Arm A and Arm B patients respectively (p value 0.277). Before treatment tracheotomy was present 12(40%) in Arm A and 3(12.5%) in Arm B (p value 0.034). Maximum subcutaneous tissue late toxicity lies in range of grade II 10(33.3%) in Arm A and 8(33.3%) Arm B patients (p value 0.874). Tumor response at 6 months CR 13(43.3%), 10(45.5%) PR 7(23.3%), 2(9.1%) and SD 0(0), 3(13.6%) in arm A and Arm B respectively (p value 0.187). Death was in 3(10%) and 1(4.5%) patients and lost to follow up were 7(23.3%) and 6(27.3%) in Arm A and B. Overall survival(OS) at 2 months, At 6 months, At 1 year with Mean  $\pm$  SD in arm A was 100, 96.4  $\pm$  3.5, 71.8  $\pm$  11.1 and in Arm B was 95.8  $\pm$  4.1, 86.8  $\pm$  7.1, 65.1  $\pm$  19.5 respectively (p value 0.516). Disease free survival (DFS) at 6 months with Mean  $\pm$  SD in Arm A was 61.1  $\pm$  13 and in Arm B was 70.7  $\pm$  12.1 respectively (p value: 0.819).

## DISCUSSION

Cancer larynx is best managed in a multidisciplinary setting.<sup>4,5,6</sup> Surgery, radiation therapy, chemotherapy and more recently biologic therapy are often employed in various combinations in an attempt to eradicate both clinically apparent and occult disease. The goals of treatment includes maximising tumor control while maintaining function and quality of life. Most patients present with locally advanced disease and multimodality organ conserving therapy is often employed for these patients based on results of multiple phase III clinical trials. Surgery was once the mainstay of treatment for all resectable cases of head and neck cancer but lead to significant morbidity. Radiotherapy had been reserved for unresectable or palliative cases, but this treatment modality has overtaken surgery as the primary local treatment option for most head and neck cancers, largely in the setting of organ conservation approaches to treatment.<sup>7,8</sup> The ultimate goal is to enhance the therapeutic ratio in the treatment of head and neck cancers through a collaborative, multidisciplinary effort, leading to improved cure rates while decreasing long term morbidity and optimizing patient's quality of life. Treatment selection is based on the tumor extension, physician's recommendation and patient's preference.

There are some factors that influence the laryngeal tumor control probability of RT. To improve tumour control total dose increase by hyperfractionated radiotherapy, shorter treatment time by accelerated radiotherapy and radiation enhancement by concurrent radiotherapy have been conducted but these protocols increased adverse effects. The DAHNAKA trial of 6days/week treatment protocol that completes treatment in 39 days improved outcome compared with the conventional 5days/week treatment protocols that takes 46 days. However, it is not widely used because of the inconvenience of the necessary weekend visit and at times hampers the up keepment of machines. In such situations, several studies have reported that daily fractionation dose higher than 2Gy improved local control. In our study, maximum number of cases were in the age group 41-70 years, 90% in arm A and approximately 87.6% in arm B, (Austen et al 1982, Bethesda 1991).<sup>9,10</sup> The disease was found to be common in males as compared to female. Arm A male 93.3% : female 6.7% and arm B male 95.8% : female 4.2%. This pattern is in accordance with the available literature (V H Coupland, 2009).<sup>77</sup> Disease is less common below 20 years, this may be because of lesser exposure to addiction agent. In our study, only 11% of cases had no addiction history. 89% of cases had addiction history in which 66.6% had history of bidi/cigarette

smoking, 51.8% had tobacco/pan masala chewing history. This result was comparable according to (Mehta et al 1982, Dave et al 1991, Gupta et al 1994, Bundgard 1994<sup>18,17</sup>, Jayant et al, 1977).<sup>11</sup> In our study, the patient analysis was done according to TNM staging and it revealed that majority of patients were of stage IV (89%) as compared to stage III (11%). Thus even now patients in our country are unable to come in early stage of disease as even educated patients are highly ignorant about their health and majority of patients gave history of treatment by some ayurvedic or homeopathic remedy for months resulting in progression of disease to such an advanced stage. In both the arms that is conventional chemoradiotherapy arm and hypofractionated chemoradiotherapy arm, all the biosocial co-relates of study subjects were balanced. RTOG 90-11 used Cisplatin on three weekly basis and the results were far better in terms of response, survival and larynx preservation. In our study also we used three weekly Cisplatin in both the arms at the rate of 100 mg/m<sup>2</sup> three weekly. Dose fractionation along with overall treatment time are expected to be key factors in the outcome of definitive radiotherapy for locally advanced carcinoma larynx. Schedules with shortened overall treatment have the potential advantage of minimising the impact of accelerated repopulation. Overall treatment time is known to be related to locoregional control for head and neck cancers. An acceleration in treatment time can be achieved by either hypofractionation or hyperfractionation with multiple treatments per day. Radiological modelling based upon the linear quadratic model suggests similar log<sub>10</sub> cell kill and late-effects BED for a schedule of 60Gy in 20 fractions over 28 days compared with conventionally fractionated schedule of 70 Gy in 35 fractions over 49 days. For late effects (using alpha/ beta of 3Gy for late responding tissues) the BED for a schedule of 60Gy in 20 fractions is 120Gy and for a schedule of 70Gy in 35 fractions is 116.6Gy respectively. In this study, we focused on conventional vs. Hypofractionated regimen and it revealed 76.7% patients in arm A and 75% patients in arm B reached complete response after treatment. 23.3% patients in arm A and 4.2% in arm B showed partial response for which either the patients were advised salvage surgery or salvage chemotherapy according to patients will. 12.5% stable disease and 8.3% (2pts) deaths were notes in arm B. (P value 0.023, chi square value 9.56).= There is an added advantage in terms of the study group, for reducing overall treatment time considerably as treatment is complete in 4 weeks in place of 7 weeks in the conventional radiotherapy group which is an extremely important aspect as far as Indian population especially rural areas is concerned.

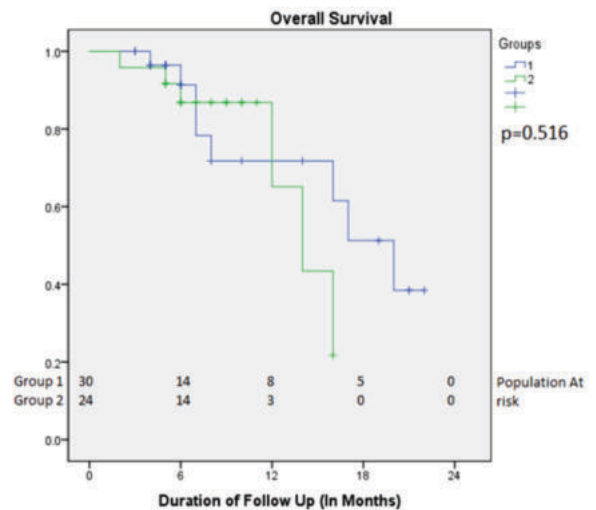


Figure 1

Another significant advantage is of decreasing workload on radiotherapy machines because treatment duration is reduced. This extrapolates into the reduction of waiting list of patients for radiotherapy. Another important point was the incidence of acute radiation reactions that was observed in both the groups. The incidence and intensity of acute RT reactions was little more in hypofractionated radiation arm as compared to conventional radiation arm but the difference was not statistically significant. Most of the patients tolerated acute RT reactions easily when supportive treatment in the form of intravenous fluids with multivitamins and amino drip infusion along with high protein diet was given. In both the groups RT reactions were negligible in 1st week and subsequently increased in 4th to 5th

week in Arm B and 3<sup>rd</sup> week in Arm A. OS at 2 months, 6 months and 1 year is appears to be more in hypofractionated arm than conventional arm; although P value is not significant. DFS at 2 months and 6 months appears to be more in conventional arm than hypofractionated arm; P value is not significant. Late toxicities in terms of skin and subcutaneous tissue appears to be slightly more in hypofractionated arm at 6 month; P value not significant. If greater daily fraction dose increased adverse effects, we could not use a greater dose. But according to our data, no severe adverse effects have been observed. Mendenhall et al<sup>12</sup> reported that higher daily fraction doses resulted in higher local control rates without a significant increase in acute adverse effects. Hypo fractionated radiotherapy with concurrent cisplatin every 3 weeks is a reasonable alternative to the standard fractionated regimen with concurrent cisplatin offers advantages of decreased overall treatment time, better compliance, decreased hospital stay with comparable response rate and toxicity profile.

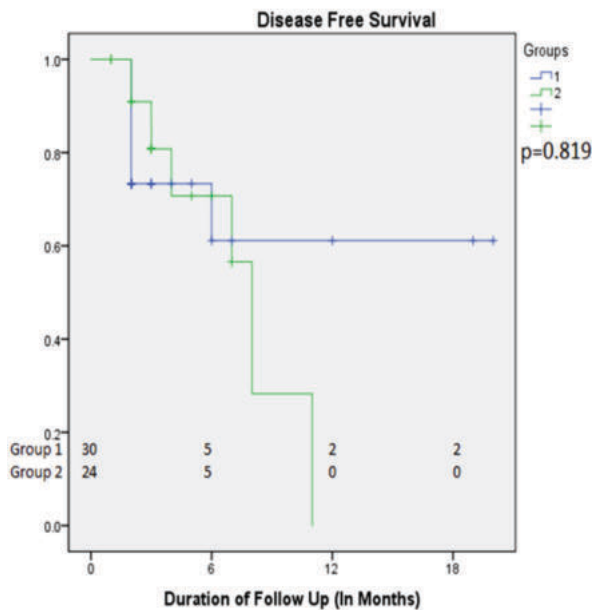


Figure 2

Table 1. Patients Characteristics

Age Groups		Arm A (N=30)	Arm B (N=24)	p value	Chi Square value
31-40	(Percentage)	2 (6.7)	2 (8.3)	0.997	0.167
41-50		6 (20)	4 (16.7)		
51-60		9 (30)	7 (29.2)		
61-70		12 (40)	10 (41.7)		
>70		1 (3.3)	1 (4.2)		
Staging		Arm A (N=30)	Arm B (N=24)	p value	Chi Square Value
T3	(Percentage)	3 (10)	5 (20.8)	0.265	1.24
T4		27 (90)	19 (79.2)		
Staging		Arm A (N=30)	Arm B (N=24)	p value	Chi Square Value
N0	(Percentage)	12 (40)	12 (50)	0.665	1.57
N1		6 (20)	3 (12.5)		
N2		11 (36.7)	7 (29.2)		
N3		1 (3.3)	2 (8.3)		
Overall Staging		Arm A (N=30)	Arm B (N=24)	p value	Chi Square Value
III	(Percentage)	3 (10)	3 (12.5)	0.682	0.765
IVa		25 (83.3)	19 (79.2)		
IVb		2 (6.7)	2 (8.3)		
Gender Distribution		Arm A (N=30)	Arm B (N=24)	p value	Chi Square Value
Males	(Percentage)	28 (93.3)	23 (95.8)	1	0.159
Females		2 (6.7)	1 (4.2)		
Ryles Tube		Arm A (N=30)	Arm B (N=24)	p value	Chi Square Value
Yes	(Percentage)	6 (20)	2 (8.3)	0.277	1.438
No		24 (80)	22 (91.7)		

Overall Treatment Time		Arm A (N=34)	Arm B (N=34)	p value	Chi Square Value
<6 weeks	Number (Percentage)	24 (80)	0 (0)	<0.001	32.16
6 – 8 weeks		4 (13.3)	9 (37.5)		
>8 weeks		2 (6.7)	15 (62.5)		
Addictions		Arm A (N=30)	Arm B (N=24)	p value	Chi Square Value
Smoking	Number (Percentage)	19 (63.3)	17 (70.8)	0.56	0.338
Tobacco		17 (56.7)	11 (45.8)		
Skin Reaction		Arm A (N=30)	Arm B (N=24)	p value	Chi Square Value
I	Number (Percentage)	27 (90)	22 (91.7)	0.652	0.854
II		2 (6.7)	2 (8.3)		
III		1 (3.3)	0 (0)		
Mucosal Reaction		Arm A (N=30)	Arm B (N=24)	p value	Chi Square Value
I	Number (Percentage)	8 (26.7)	14 (58.3)	0.063	5.54
II		20 (66.7)	9 (37.5)		
III		2 (6.7)	1 (4.2)		
Tracheostomy		Arm A (N=30)	Arm B (N=24)	p value	Chi Square Value
Yes	Number (Percentage)	12 (40)	3 (12.5)	0.034	5.026
No		18 (60)	21 (87.5)		

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