

Locoregional Control and Toxicity Profile of Six Fractions of Radiotherapy per Week in Locally Advanced Squamous Cell Carcinoma of Head and Neck

Kunhalan Kutty C.K¹, Binesh P², Jayaraman M.B³, Prasanth C.C⁴

ABSTRACT

Introduction: Treatment of locally advanced head and neck squamous cell carcinoma (LAHNSCC) is a challenging proposition. Prolongation of overall treatment time has shown to increase the failure rates. We aimed to shorten the overall treatment time by using accelerated fractionation-six fractions of radiation per week instead of 5 fractions. Study aimed to assess the response and toxicity profile of six fractions of radiation per week in LAHNSCC.

Material and Methods: Stage III and IV LAHNSCC selected for radiation treatment alone with Co60 teletherapy machine. The total dose of 66Gy /33 fractions – 6 fractions per week, from Monday to Saturday over a period of 5.3 weeks.

Results: All the 45 patients received the planned treatment. All patients completed the treatment in stipulated overall treatment time. At the 6th week of completion of radiation, responses were assessed. Out of 45 patients, 29 had the complete response (64.4%), and 12 had the partial response (26.66%), no response seen in 3 patients (6.66%) and progressive disease in 1 patient (2.22%). Patients reviewed twice weekly for assessing the toxicities. Major toxicities were mucosal and dermatological. 38 patients out of 45 had grade I and II skin reactions (83.6%), and 7 patients developed grade III skin reaction (16.4%). 29 out of 45 patients developed grade I and II mucosal reactions (65%) 16 out of 45 (35%) patients had grade III mucosal reactions. None of the patients developed grade IV skin or mucosal reactions.

Conclusion: This study shows that pure accelerated Radiotherapy 6 fractions per week in LAHNSCC is feasible and found to enhance the response rate with tolerable toxicities.

Keywords: Locally Advanced Head and Neck Squamous Cell Carcinoma, Radiation Treatment, Pure Accelerated Radiotherapy, Overall Treatment Time, Treatment Response, Toxicity Profile.

INTRODUCTION

The incidence of squamous-cell carcinoma of the head and neck (HNSCC) is increasing, and it is now the fourth most common malignant disease in the world, with more than 70% of cases occurring in the developing world.¹ HNSCC is a locoregional disease confined to a primary tumor and the regional lymph nodes; distant metastases are rarely seen at the time of diagnosis. Head and neck cancers are the commonest neoplasms seen in India accounting for significant morbidity and mortality. Every year about 700,000 to 900,000 new cases are detected in India, accounting for one-fourth of male and one-tenth of female cancers.^{1,2} Approximately 70%-80%

are diagnosed with the locally advanced disease with lymph node involvement in up to 30%-50% of cases.^{3,4} Because of the high incidence of advanced disease at presentation and local failure rates of 50%-60% the management of head and neck carcinomas is a challenging proposition.⁵

Study aimed to assess the response in locally advanced squamous cell carcinoma of head and neck for accelerated radiotherapy-six fraction per week schedule and to determine the acute toxicity rate of accelerated fractionation

MATERIAL AND METHODS

This prospective study was conducted in the Department of Radiotherapy, Medical College, Trivandrum in patients with locally advanced squamous cell carcinoma head and neck region. Only those patients who required external, radical radiotherapy as the primary line of management were included in this study. After complete history taking and physical examination, the patients underwent baseline investigations including complete blood count, kidney function, and liver function tests. Chest X-ray and X-ray soft tissue neck lateral view and X-ray PNS etc. depending on the site of a primary tumor. Investigations such as barium swallow, ultrasound abdomen, and CT scan were done if required to rule out distant metastasis or to assess the extent of the disease. After examination and investigations, all patients were staged according to International TNM classification of AJCC 2010.

Inclusion Criteria

1. Histologically proven squamous cell carcinoma of head and neck (Oral cavity, pharynx and larynx) - locally advanced stage III-IV as per AJCC 2010

¹Assistant Professor, Department of Radiotherapy, Government Medical College, Kozhikode, ²Assistant Professor, Department of Radiotherapy, Government Medical College, Kozhikode, ³Associate Professor, Department of Radiotherapy, Government Medical College, Thrissur, ⁴Assistant Professor, Department of Radiotherapy, Government Medical College, Kozhikode, Kerala, India

Corresponding author: Dr. Binesh P, Assistant Professor, Department of Radiotherapy, Government Medical College, Kozhikode, Kerala, India

How to cite this article: Kunhalan Kutty C.K, Binesh P, Jayaraman M.B, Prasanth C.C. Locoregional control and toxicity profile of six fractions of radiotherapy per week in locally advanced squamous cell carcinoma of head and neck. International Journal of Contemporary Medical Research 2018;5(8):H5-H9.

DOI: <http://dx.doi.org/10.21276/ijcmr.2018.5.8.23>

2. Age above 18 years and less than 70 years-both males and females
3. ECOG performance status 0-2
4. Eligible patients were candidates for primary curative radiotherapy without previous or planned surgical excision of the primary tumour or lymph node
5. Patients without any serious medical condition
6. Patients without distant metastasis
7. Patients with adequate bone marrow function defined as a peripheral granulocyte count of >2000 cells/mm³, platelet count >1lakh/mm³ adequate hepatic function with bilirubin <1.5mg% and serum creatinine <1.5mg%

Exclusion Criteria

1. Previously treated patients with surgery, radiotherapy or chemotherapy,
2. Tumour classified as stage I & II
3. Presence of distant metastasis
4. Existence of multiple malignancies
5. Patients with ECOG performance status >2
6. Participation in any other related clinical study during the past or present, and patients having some associated medical condition making them unsuitable for radical treatment.

External beam Radiotherapy was given using Cobalt 60 Teletherapy machine to provide appropriate photon energies. All patients were planned with proper field placement and standard treatment portals for conventional radiation designed according to the primary lesion. All the patients were treated using parallel opposed technique covering the primary tumor with its local extensions with 2cm margin and the regional lymphatic drainage areas. Treatment portals tailored according to the need of the individual patient. Wedges were used wherever necessary to ensure dose homogeneity. Treated in the supine position with neck rest and shoulder retraction. Reproducibility ensured by using the immobilisation-orfit shell. The shrinking field technique was used, and the spinal cord was excluded from the radiation field after a dose of 44 Gy. Planned to receive a total radiation dose of 66 Gy in 33 fractions over 5.3 week's period with a dose of 200 cGy per fraction dose in six days a week schedule from Monday to Saturday. Treatment distance of 80 cm SSD. During the treatment period, all patients were examined weekly for radiation reactions over the skin, oral mucosa by the RTOG radiation toxicity scoring. Similarly, patients were evaluated for hoarseness, dysphagia, gastrointestinal toxicity like nausea, vomiting, and hematological toxicity. Patients were evaluated for the effects of treatment on the primary tumor site and regional lymph nodes. The usual statistical methods had been utilized to assess, analyze, and evaluate the so obtained observations and data.

Patients were evaluated for response to treatment both at the primary site and lymph node areas immediately after treatment and 6 weeks of completion of treatment.

Criteria used for the assessment of response

- CR- complete response is the complete disappearance of all measurable disease

- PR- partial response is the regression of more than 50% measurable disease
- NR- no response is the regression of less than 50% of measurable disease
- PD- progressive disease is the progression of the initial disease

STATISTICAL ANALYSIS

Descriptive statistics like mean and percentages were used for the analysis.

RESULTS

Patients with stage III and IV (nonmetastatic) SCC of head and neck excluding carcinoma Nasopharynx were selected. A total of 45 patients satisfied the eligibility criteria.

The socio-demographic and clinicopathologic characteristics of all the 45 patients with loco-regionally advanced SCCHN receiving accelerated radiotherapy were consistent with previously published head and neck literature. Although

Primary site	Complete response	%
Oropharynx	10	66.66
Hypopharynx	4	50
Larynx	10	71.42
Oral cavity	5	62.5

Table-1: Response according to site

Response according to T stage	Complete response		Partial response	
	Number	%	Number	%
T1	2	100	0	0
T2	7	77.77	2	22.22
T3	20	74	7	26
T4	0	0	3/7	42.85

Table-2: Response according to T stage

Control of Primary	Number	%
Complete response	29	64.44
Partial response	12	26.66
No response	3	6.66
Progressive disease	1	2.22

Table-3: Control of the Primary At 6th week

Response according to nodal stage	Complete response		Partial response	
	Number	%	Number	%
N1	12	75	4	25
N2	12	60	8	40
N3			1	100

Table-4: Response according to nodal stage

Response according to composite staging	Complete response		Partial response	
	Number	%	Number	%
Stage III	14	73.68	5	26.31
Stage IV	16	61.53	10	38.46

Table-5: Response according to composite staging

medical co-morbidities consistent with the age-pyramid were prevalent, they were not significant enough in the large majority such as active tuberculosis, uncontrolled hypertension or diabetes mellitus, or nephropathy.

Out of 45 patients, 15 (33.3%) had Carcinoma oropharynx, 14 (31.1%) had ca larynx, 8 (17.7%) had Ca hypopharynx, and 8 (17.7%) had Ca oral cavity (table-1).

The majorities (37.7%) of the patients were within the age group 50 – 59 years, 37 patients (83.5%) were males, and 8 (16.5%) patients were females, 37 male patients 30 are chronic smokers, and 20 are alcoholics. Among 8 females one patient was a smoker, and two of them used to chew betel and areca nut. Out of 45 patients 2 (4.5%) patients had T1 tumour, 9 (20%) had T2 tumour, 27(60.0%) had T3 tumour and 7 patients (15.5%) had T4 tumour, 8 (17.7%) patients had N0 status, 16 (35.5%) had N1 status, 20 (44.3 %) had N2 status and 1 (2.2%) patient had N3 status. Out of 45 patients, 19 patients (42.2%) were stage III, and 26 patients (57.7 %) were stage IV.

Skin reactions

The various acute reaction effects on the skin as per RTOG Level observed during treatment. During the third week, 63% of patients developed definite erythema while 13.3% patients developed erythema with desquamation. Dry desquamation and epilation (RTOG Grade I) were observed in 16.6% of patients, during the 4th week of the treatment. During the 5th week, patchy moist desquamation (RTOG Grade 2) was observed in 10% of patients. During sixth week Grade, 3 reactions were noted in 16.4% of patients, while Grad 1& 2 were observed in 83.6% patients. No patient developed Grade 4 or higher level of reactions. Although the patients developed skin reactions more rapidly and in large number, however, they were manageable

Mucosal reaction

At the end of the second week, 53.3% of the patients developed mild erythema (RTOG Grade 1). During the 3rd week of treatment, the number of patients had definite erythema. During the 4th week, definite erythema and patchy mucositis (Grade2) was seen in 33.3 % of patients.

During the 4th week, 11 patients developed patchy mucositis in more than half of the field. At the end of 5th week of treatment, patients had grade 3 mucosal reactions. At the end of treatment, 35% of patients had confluent mucositis. However, all the patients in the study group were able to complete the radiation treatment during the planned period. Majority of patients managed with analgesics, antibiotics, and proper hydration. Eight patients with Grade 3 reaction required admission and parenteral medications. Most of the reported literature on accelerated fractionation showed higher grades of mucositis compared to conventional fractionation.

The RTOG acute grade 3 or worse mucositis was seen in 16(35%) patients. Grade 3 or more skin reaction was seen in 7 (16.4%) patients. Mild to moderate nausea and vomiting occurred in almost all patients despite anti-emetic prophylaxis

Dry mouth and difficulty in swallowing were seen in almost

all patients and around half of the patients had hoarseness.

All patients completed the planned treatment without interruption 5 patients required hospitalization and parenteral medication. In 10 patients Ryle's tube feeding was required due to odynophagia.

64.4% (29/45) patients had complete clinical response while 26.66 % (12/45) patients had the partial clinical response. No response in 3 patients and progressive disease in one patient at the end of the first month. All patients (2/2) in T1 stage, 7/9 (77.77%) patients in the T2 stage, 20/27 (74%) patients in the T3 stage had the complete clinical response (table-2). Complete response rates were 66.66% (10/15) for primary oropharynx tumors, 50% (4/8) for hypopharynx, 71.42% (10/14) for larynx and 62.5% (5/8) for oral cavity.

Control of node at 6th week

Nodal response to treatment was analyzed separately. 12/16 (75%) patients in the N1 stage, 12/20 (60%) patients in the N2 stage and none in the N3 stage had the complete clinical response (table-3).

Control of the disease stage wise

Out of 19 patients with stage III disease, 14 patients (73.68%) had complete clinical response and out of 26 patients in with stage IV disease 15 patients (57.69%) had complete clinical response during at six weeks after completion of radiation. No response was seen in one patient with stage III and two patients with stage IV, and progressive disease in one patient with stage IV (table 4,5).

DISCUSSION

The present study was conducted to evaluate the six fractions per week radiotherapy schedules in the locally advanced head and neck carcinoma patients. The study was meant to evaluate the feasibility of six fractions per week (pure accelerated hyperfractionation) radiation schedules regarding locoregional control of the tumor and radiation-induced acute toxicities. The age and sex distribution and the addiction patterns also correlated with data in the literature which reports peak incidence in 50-70 years, a pre-dominant male predilection and association with smoking, alcohol, and tobacco. Patients with all the three risk factors have a high risk of developing carcinoma. Smoking was to be a significant risk factor in the development of carcinoma. Common sites of primary are oropharynx, larynx and oral cavity. All patients completed planned irradiation without treatment interruption. In our study, most of the skin toxicities are Gr-I & II in 83.36%, and Grade III occurs in 16.4% of patients. 65% of the patients developed Grade I & II mucosal reactions, and Grade III occurs in 35%. Laryngeal Mucosal toxicity (Gr-I 26.6% Gr II 56.6% and Gr III 17%). Odynophagia occurs in 86.66% of patients. All these did not result in treatment break. Only eight patients required hospitalization for parenteral medication. Other patients managed with oral analgesics, antibiotics, and proper hydration. All the patients were followed up after completion of treatment. Complete response was 64.4% at the end of the sixth week of follow up. Partial response was 26.66%. Overall response (CR+PR)

observed in 91.06% of patients. Complete response is more in primary site compared to node. T1 and T2 tumors with node involvement have the better response than T3, T4 tumors.

Overgaard et al. conducted a comparative study in squamous cell carcinoma head and neck, by giving 66 Gy either 5 or 6 fractions per week. After a follow-up time of 5 years, locoregional control rate was 66% for the patient who underwent 6 fractions per week compared with 57% for patients who underwent 5 fractions per week schedule. The benefit of tumor control resulted in a significantly better overall disease-specific survival (65% vs. 72%) for 5 vs. 6 fractions per week.^{5,4}

Various studies and publications involving management of head and neck cancer reveal prolongation of overall treatment time to adversely affect the cure rates. Hence to improve the cure rates, many forms of altered fractionation radiotherapy have been tried.⁶ One among the altered fractionation is accelerated radiotherapy where the dose per fraction is 200 cGy, and the total dose remains the same which is 66Gy, but the overall treatment time is shortened by one week. This reduction in treatment time not only improves the cure results but also decreases the period of hospital stay, thereby enabling us to treat more patients where there is an increased load of patients in an institution like ours. Accelerated radiotherapy applied to squamous cell carcinoma of the head and neck yields better locoregional control compared to published and established conventional schedules with identical dose and fractionation.

This finding is in agreement with several similar but smaller randomized studies.⁷⁻¹⁰ Accelerated regimens, however, increase the treatment-related morbidity, and if this becomes severe, it could also raise the frequency of late radiation side effects. In this study, we did see the increase in acute mucositis, but it was transient and manageable. Thus the window of opportunity for the benefit of acceleration is narrow and with the applied radiation technique a one-week reduction seems to be the optimum balance between improved tumor control and avoidance of excess morbidity. This study was based on the Danish DAHANCA 6 trial.¹⁰ In this study, patients were treated with 6 fractions per week to a total dose of 66Gy which reduced the overall treatment time by 1 week. Withers et al., and Bernier J et al and Thames et al showed that a dose of 0.48 Gy per day was recovered by tumor during fractionated radiotherapy of HNSCC.^{6,11,12} This was the reason why in our study in which overall treatment time was reduced by 1 week, produced higher response compared to previously published conventional fractionation studies. By reducing overall treatment time by 1 week, the 'Dose recovery factor' of 1.33Gy was avoided.

The effect of acceleration on local control was entirely related to better response in the tumor site than the nodal response which was shown in DAHANCA 6 study. The corollary of this finding is a better effect of acceleration in laryngeal tumors, since these tumors have less nodal involvement than those in the pharynx or oral cavity.

The concept of effective doses was suggested by Jack Flower based on LQ model. Based on the calculations we

have delivered 72.4Gy in 5.3 weeks, which is equal to 70Gy in conventional fractionation in 7 weeks. The Danish trial showed the benefit of accelerated radiotherapy in younger patients. In our study, we have opted patients up to 70yrs. The benefit shown here is consistent with the Danish study.¹⁰ Hliniak et al. did a multicentre trial by two fraction regime compared with the conventional regime in 395 patients with laryngeal cancer patients. Conventional arm received 66Gy in 33 fractions over 45 days. Accelerated fractionation arm received 66Gy in 33 fractions over 38 days. AF showed better locoregional control and the better prognosis compared with conventional arm.¹³ As compared with control group and other reference studies, the result of the present study also showed significant improvement in local control.

CONCLUSION

This data shows that it is feasible to do Accelerated Radiotherapy with manageable, although substantial, toxicity. The compliance to therapy is high, and the local response achieved with Accelerated Radiotherapy is significant. The hospital stay is reduced. Hence it is an effective alternate regimen in centers with high work load and with limited resources. It also compares well with the available literature. Large sample size is required to achieve a statistically significant result with this protocol.

REFERENCES

1. Parkin DM, Muir CS, Whelam SL, Gao VT, Ferlay J and Powell J. eds. Cancer Incidence in Five continents Volume VI. IARC Scientific Publications No.147, Lyon, France. 1997.
2. Yeole BB, SanKaranarayanan R, Sunny MscL, Swaminathan R, Parkin DM. Survival from head and neck cancer in Mumbai (Bombay), India, Cancer 2000;89 Suppl 2:437-44.
3. Al- Sarraf M. Head and neck cancer: Chemotherapy concepts. *SeminOncol* 1988; 15:70-85.
4. Stupp R, Weichselbaum RR, Vokes EE. Combined modality therapy of head and neck cancer. *SeminOncol* 1994; 21:349-58.
5. Ervin TJ, Clark JR, Weichselbaum PR. An analysis of induction and adjuvant chemotherapy in the multidisciplinary treatment of squamous cell carcinoma of head and neck. *J ClinOncol* 1987;5:10-20.
6. Withers HR, Taylor JM, Maciejewski B. The hazard of accelerated tumorclonogen repopulation during radiotherapy. *ActaOncol* 1988; 27: 131-146.
7. RTOG Phase III randomized study to compare hyperfractionated and two variants accelerated FuKK, Pajak TF, Trotti A, et al: A RTOG fractionation to standard fractionation radiotherapy for squamous cell carcinoma of head and neck First report of RTOG 9003. *Intl J Radiation OncolBiol Physics* 2000; 48:7-16.
8. Ashok K Chauhan and et al Six fractions of radiotherapy in locally advanced head and neck cancers-The internet Journal of Head and neck surgery™ ISSN:1937-819X, 2010 volume 4
9. Wang CC. Local control for oropharyngeal carcinoma after two accelerated hyperfraction radiation therapy scheme. *Int J RadatOncolBiolPhys* 1988;144:209-10.

10. Overgaard J, Hansen HS, Specht L, Overgaard M, Grau C, Andersen E, et al. Five compared with six fractions per week of conventional radiotherapy of squamous cell carcinoma of head and neck:DAHANCA 6& 7 randomised controlled trial. *Lancet* 2003; 362:933-40.
11. Bernier J, Bentzen SM. Altered fractionation and combined radio-chemotherapy approaches: pioneering new opportunities in head and neck oncology. *Eur J Cancer* 2003; 39: 560-571.
12. Thames HD, Withers HR, Peters LJ, et al Changes in early and radiation responses with altered dose fractionation. Implication for dose- survival relationships. *Intl J Radiat Oncol Biol Phys* 1982;8:219-226.
13. Hliniak A, Gwiazdowska B, Szukowski Z, Krazewska, Sochacka B, Mazurkiewicz M. Radiotherapy of laryngeal cancer. The estimation of therapeutic gain and enhancement of toxicity by one week shortening of the treatment time: Results of the randomized phase III multicenter trial. *Radiothe Oncol* 2000;56 Suppl: S5

Source of Support: Nil; **Conflict of Interest:** None

Submitted: 16-07-2018; **Accepted:** 11-08-2018; **Published:** 31-08-2018