IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 6 Ver. IV (June. 2017), PP 80-83
www.iosrjournals.org

"Hypofractionated Accelerated Radiotherapy Compared with Conventional Radiotherapy of Squamous Cell Carcinoma of Head and Neck with Concurrent Cisplatin"

Neeraj Sharma[1], R.K.Spartacus[1], Aseem Rai Bhatnagar[1], Kartick Rastogi, R.K.Panday, [2]Rohitashwa Dana[1], Sandeep Jain[1], Sandeep Bhaskar[1]

[1](Department of Radiotherapy/Linear Accelerator Centre, SMS Medical College and Attached Hospitals/ Rajasthan University of Health Sciences, India)

[2](Department of Radiotherapy, Jawaharlal Nehru Cancer Hospital & Research Centre, Bhopal, India)

Abstract:

Introduction: *Locally advanced head and neck carcinomas (HNSCC) constitute a substantial proportion of cancer patients in India. This is treated by combined multimodality which includes surgery, radiotherapy, and chemotherapy.*

Aims: *To investigate tumor response and toxicity in HNSCC using hypofractionated schedule compared with conventional fractionation.*

Material and Methods: *In conventional arm (Arm A), each patient received 70 Gy/2 Gy/fraction/7 weeks. In hypofractionated arm (Arm B), each patient received 55 Gy/2.75 Gy/fraction/4 weeks. Both arms received weekly cisplatin (40 mg/m ^{2}). The end points were tumor response, acute and late toxicities, and overall survival (OS).*

Results: *17 patients (68%) in a conventional arm (Arm A) achieved a complete response (CR) and 15 patients (60%) in hypofractionated arm (Arm B) had a CR (p=0.55). The acute skin toxicity (grade≥2) was significantly higher in Arm B than in Arm A (28% vs. 17%; $p \leq 0.001$). Grade ≥ 2 mucositis was also higher in hypofractionated arm (88% in Arm B vs. 40% in Arm A; $p \leq 0.001$). Late toxicity of grade 2 or higher was greater in hypofractionated arm. The median Overall Survival was 18 months in conventional arm versus 17 months in hypofractionated arm.*

Conclusion: *We achieved comparable tumor control in patients with HNSCC. The hypofractionated regimen was associated with increased but tolerable acute and late morbidities. The reduction in number of fractions and treatment time allows more efficient use of resources which can help avoid long waiting times in a busy center, but routine use of this hypofractionated schedule needs further studies.*

Keywords: *Head and Neck, Locally advanced, Radiotherapy, Conventional, Hypofractionation*

I. Introduction

Head and neck cancers constitute a substantial proportion of cancer patients in developing countries like India and most patients present with locally advanced disease.[1] Locally advanced squamous cell carcinoma of head and neck (HNSCC), is treated by combined multimodality which includes surgery, radiotherapy, and chemotherapy. Previous randomized controlled trials have demonstrated improvements in loco-regional tumor control from altered fractionation radiotherapy with or without chemotherapy as compared with conventional fractionation. Altered fractionation schedules improve the therapeutic ratio between tumor cell kill and normal tissue damage by exploiting the dissociation between acute and late radiation effects. Hypofractionated radiotherapy utilizes a small number of fractions with a larger dose per fraction, shortening overall treatment time compared to a conventional protocol. However, hypofractionation schedules may result in increased incidence of late complications. Although most centers adopt the conventional 2 Gray (Gy)/fraction schedule, a substantial proportion of patients in United Kingdom (UK) receive a hypofractionated prescription with larger doses per fraction, such as 55 Gy in 20 fractions (2.75 Gy/fraction). This regimen has the theoretical advantage that the treatment is completed before accelerated tumor cell repopulation becomes a significant factor. [2],[3] The objective of the present study was to investigate tumor response and toxicity in HNSCC using hypofractionated schedule compared with conventional fractionation with or without concurrent chemotherapy.

II. Material And Methods

The present study was undertaken in the patients having head and neck malignancies who attended the department of radiotherapy at Jawaharlal Nehru Cancer Hospital & Research Centre, Bhopal from March 2012 to February 2013.

Inclusion criteria

Patient with biopsy proven locally advanced [stage III & IV] Squamous Cell Carcinoma of head and neck, no evidence of distant metastases, Karnofsky's performance status greater than 60%, between 18-65 years of age, Hemoglobin >10gm%, Total WBC count >4000/mm3, platelets >1,00,000 and with signed informed consent were included.

Exclusion criteria

Patients with parotid tumours and other salivary gland tumours, any previous malignancy, unknown primary, deranged renal & liver function tests (more than twice the upper limit of normal), pregnant or lactating women or patients previously treated by chemotherapy or radiotherapy were excluded.

Treatment protocol

All the cases taken in this study were treated by external beam radiotherapy by Cobalt 60 unit or Linear Accelerator. All the patients in Arm B (n=25) received conventional regimen with 200cGy/fraction, 5 times a week for 7 weeks while all the patients in Arm A (n=25) received hypofractionated radiation therapy i.e. 275cGy/fraction, 5 times a week for 4 weeks. The fields were reduced accordingly in Phase II so as to spare the spinal cord and to boost the primary tumor and involved lymph nodes with 1.5 to 2 cm margins up to 55Gy in Arm A and 70Gy in Arm B. In both groups Cisplatin 40mg/m² starting on day 1 of radiation was repeated weekly till patient is discharged from radiotherapy. Blood counts were monitored weekly during chemoradiotherapy.

Response evaluation and toxicity grading

Treatment response was evaluated using RECIST criteria and toxicity assessment was done as per Radiation Therapy Oncology Group (RTOG) criteria.

III. Results

A total of 50 patients meeting the study criteria were included in the study with [Table 1&2].

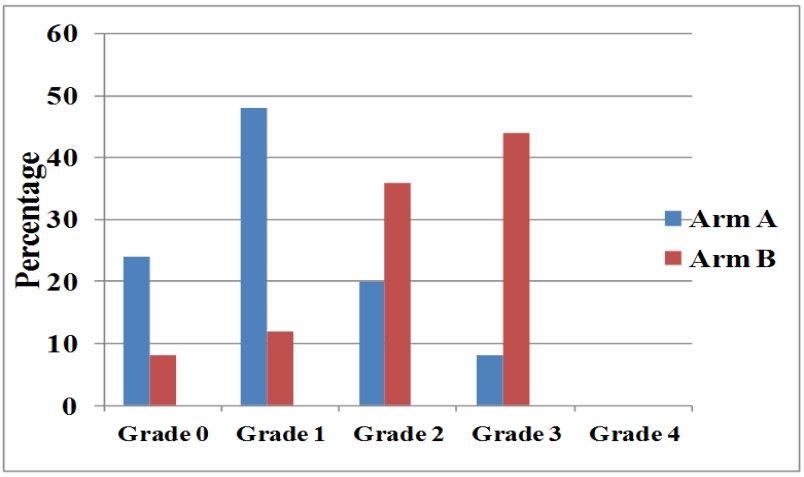
Table 1. Patient Baseline Characteristic

	Conventional arm (n=25)	Hypofractionated arm (n=25)
	Age (years)	
Range	21-72	29-67
Mean	47	44
	Sex	
Male: Female	21:4	21:4
	Site of primary lesion	
Oral Cavity	8	10
Larynx	7	8
Oropharynx	6	6
Hypopharynx	4	8

Table 2. Disease presentation (TNM)

T	Group A (conventional)				Group B (hypofractionated)				M
	N0	N1	N2	N3	N0	N1	N2	N3	
T1	0	0	0	0	0	0	0	0	M0
T2	0	1	0	0	0	0	0	0	M0
T3	1	6	6	1	2	6	5	1	M0
T4	2	0	8	0	0	2	8	1	M0

Response evaluation was done 3 months after completion of treatment and response was categorized as per RECIST criteria (version 1.1). 17 patients (68%) in a conventional arm (Arm A) achieved a complete response (CR) and 15 patients (60%) in hypofractionated arm (Arm B) had a CR. The results were statistically insignificant (p=0.55). 8 patients (32%) in Arm A and 10 patients (40%) in Arm B achieved Partial Response (PR).



Bar Diagram 1. Showing RTOG acute toxicity in Arm A and Arm B

The most prevalent acute toxicities were dermatitis, mucositis and dysphagia. The acute skin toxicity (grade≥2) was significantly higher in Arm B than in Arm A (28% vs. 17%; $p \leq 0.001$, significant). Grade ≥ 2 mucositis was also higher in hypofractionated arm (88% in Arm B vs. 40% in Arm A; $p \leq 0.001$, significant). Late toxicities were assessed at 6, 12, 18 and 24 months from start of chemoradiation. At 24 months of follow up the late toxicity of grade 2 or higher mucositis was 25% in Arm B with no patient in Arm A having late mucositis. Similarly grade 2 or higher xerostomia was 30% in Arm B and 10% in Arm A. Both these differences reach statistical significance. The median follow-up period in this study was 20 months (range 4-38 months). The median Overall Survival was 18 months in conventional arm versus 17 months in hypofractionated arm.

IV. Discussion

Our study shows that hypofractionated chemoradiotherapy for HNSCC results in similar median OS compared to conventionally fractionated chemoradiotherapy. In the meta-analysis of radiotherapy in carcinomas of the head and neck (MARCH), encompassing 15 phase III trials and 6,515 patients, there was 3.4% OS benefit at 5 years for altered fractionation versus conventional fractionation, with most benefit suggested for hyperfractionation. [4] Concomitant chemotherapy with standard fractionation has repeatedly been shown to offer improved LRC and survival. [4],[5],[6] Sanghera et al. studied 81 patients with squamous cell cancer of the larynx, oropharynx, oral cavity, and hypopharynx who received hypofractionated radiotherapy with dose of 55 Gy in 20 fractions with concurrent chemotherapy. The 2-year local control rate was 75.4%. The 2-year OS rate was 71.6%, and the 2-year Disease Free Survival rate was 68.6%. [7] A multi-institutional trial of hypofractionated intensity-modulated radiation therapy (IMRT) for early stage oropharyngeal cancer showed that hypofractionated radiotherapy without chemotherapy for early oropharyngeal cancer is feasible, achieving high tumor control rates and reduced the salivary toxicity. [8] Bakst *et al*. treated patients with carcinoma nasopharynx, using 2.34 Gy per fraction for a total of 70.2 Gy and treatment was well-tolerated. [9]

Roy et al. showed that with a median follow-up of 17 months the Locoregional Control (LRC) rate was nearly similar for hypofractionated group in comparison with a conventional group . Hypofractionation is an alternative to conventional regimens with a shorter treatment time but with concerns about the late toxicities. Its development should not be at the expense of decreased LRC or unacceptable late toxicity. [10][11],[12],[13] In our study, similar number of patients completed the treatment as per the protocol without any interruptions. In both the groups. Significant differences in late effects were noted indicating that increased dose per fraction (2.75 Gy vs. 2 Gy) influenced late radiation-related morbidity. With a lower biologic dose in terms of late reactions compared with 70 Gy in 35 fractions (using α/β ratio=3 in LQ model), this hypofractionated schedule was associated with greater long-term toxicity. Acute morbidity such as mucositis, dermatitis, and dysphagia persist longer in patients who underwent hypofractionated treatment (Arm B).

.

V. Conclusion

We can conclude that reducing the overall treatment time by increasing dose per fraction while maintaining the Biological Equivalent Dose (BED) results in comparable tumor control in patients with HNSCC. This hypofractionated regimen is associated with increased but tolerable acute and late morbidities. The reduction in number of fractions and treatment time allows more efficient use of resources which can help avoid long waiting times in a busy center, but routine use of this hypofractionated schedule needs further studies.

References

[1] http://globocan.iarc.fr/Pages/fact_sheets_population.aspx

[2] James ND, Robertson G, Squire CJ, Forbes H, Jones K, Cottier B, *et al* A national audit of radiotherapy in head and neck cancer. Clin Oncol (R Coll Radiol) 2003;15:41-6.

[3] Williams MV, James ND, Summers ET, Barrett A, Ash DV, Audit Sub-Committe, Faculty of Clinical Oncology, *et al*. National survey of radiotherapy fractionation practice in 2003. Clin Oncol (R Coll Radiol)2006;18:3-14

[4] Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, *et al.* Hyperfractionated or accelerated radiotherapy in head and neck cancer: A meta-analysis. Lancet 2006;368: 843-54.

[5] Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: Three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 2000;355:949-55.

[6] Pignon JP, le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4-14.

[7] Sanghera P, McConkey C, Ho KF, Glaholm J, Hartley A. Hypofractionated accelerated radiotherapy with concurrent chemotherapy for locally advanced squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2007;67:1342-51.

[8] Eisbruch A, Harris J, Garden AS, Chao CK, Straube W, Harari PM, *et al.* Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). Int J Radiat Oncol Biol Phys 2010;76:1333-8.

[9] Bakst RL, Lee N, Pfister DG, Zelefsky MJ, Hunt MA, Kraus DH, *et al.* Hypofractionated dose-painting intensity modulated radiation therapy with chemotherapy for nasopharyngeal carcinoma: A prospective trial. Int J Radiat Oncol Biol Phys 2011;80:148-53.

[10] Yu E, Shenouda G, Beaudet MP, Black MJ. Impact of radiation therapy fraction size on local control of early glottic carcinoma. Int J Radiat Oncol Biol Phys 1997;37:587-91.

[11] Nishimura Y, Nagata Y, Okajima K, Mitsumori M, Hiraoka M, Masunaga S, et al. Radiation therapy for T1, 2 glottic carcinoma: Impact of overall treatment time on local control. Radiother Oncol 1996;40:225-32

[12] Agrawal A, deSilva BW, Buckley BM, Schuller DE. Role of the physician versus the patient in the detection of recurrent disease following treatment for head and neck cancer. Laryngoscope 2004;114:232-5.

[13] Nakamura K, Kodaira T, Shikama N, Kagami Y, Ishikura S, Shibata T, et al. Accelerated fractionation versus conventional fractionation radiation therapy for glottic cancer of T1-2N0M0 Phase III study: Japan Clinical Oncology Group study (JCOG 0701). Jpn J Clin Oncol 2008;38:387-9.