

Original Research Article

Concurrent Chemoradiation By Conventional Fractionation Versus Concomitant Boost Radiation In Locally Advanced Squamous Cell Carcinoma Of Head And Neck

Abstract:

Introduction: Most of the patients of head and neck cancer present with advanced stage disease. Randomized studies points to improved therapeutic ratios with altered fractionation schedules with no increase in late toxicity. There is paucity of data regarding results of altered fractionation from Indian subcontinent.

Material and Method: Sixty patients of histologically proven stage III-IV-A oropharyngeal, laryngeal & hypopharyngeal carcinoma were randomized in two arms. Control arm was treated with conventional fractionation whereas study arm received concomitant boost, both with weekly chemotherapy. Response and toxicity profile was assessed at 6, 12 and 24 weeks post treatment.

Result: Most of the patients presented in 5th - 6th decade of life with oropharynx being the most common site. Majority of patients in both the arms presented with stage IVA disease. Loco-regional control at both primary and nodal sites was similar in both the arms on follow-up. Nodal involvement and stage at presentation adversely affected the outcome. Mucositis was the most common acute toxicity observed and was significantly more in the study arm ($p=.0014, SS$). Late toxicity (laryngeal edema, subcutaneous fibrosis, hoarseness of voice) was comparable in the two arms.

Conclusion: In patients with locally advanced unresectable head and neck carcinoma, altered fractionation with concomitant boost is a feasible schedule with acceptable toxicities. The compliance to therapy is high, and the loco-regional control achieved compares favourably with concurrent chemoradiation by conventional fractionation with weekly cisplatin. However pooling of data from different centers has been advocated to derive conclusive results.

Keywords: Squamous cell carcinoma, concomitant boost, head & neck

Introduction

Head and neck Cancer remain a potential health problem in the developing world and is the sixth most common cancer worldwide. ¹The incidence is high in India contributing around 22% of the total head and neck cancers, because of certain habits like oral intake of tobacco, betel nut chewing, pan masala, poor oral hygiene and poor diet. ²

About two-third of patients with squamous cell carcinoma of the head and neck present with advanced stage disease. Distant metastases at initial presentation are uncommon, arising in only 10% of patients ³. Selection of appropriate treatment depends on tumor site, extent of tumor, patient nutritional status, concomitant health problems, social and logistic factors, and patient preference.

Unfortunately in India most of the patients present with advanced carcinomas which are unresectable and loco-regionally advanced. The pattern of failure even after a successful primary treatment is loco-regional, emphasizing the need for aggressive loco-regional treatment. To improve loco-regional tumor control in locally advanced non-metastatic, squamous cell carcinoma of the head and neck (SCCHN), altered fractionated regimens ⁴⁻⁷ and combined RT and chemotherapy (CT), with or without surgery, ⁸⁻¹⁰ have been used.

Evidence from both retrospective and randomized studies points to improved therapeutic ratios with altered fractionation schedules ¹¹ with no increase in late toxicity. Positive results from the concurrent chemoradiotherapy trials, led to the combination of altered fractionation and concurrent chemotherapy in patients with locally advanced head and neck cancers in an attempt to further improve both local control and overall survival.

Thus the present study aims to compare the efficacy and toxicity of concomitant boost with conventional fractionated radiotherapy using weekly concurrent cisplatin in loco-regionally advanced head and neck squamous cell carcinoma.

Material & Methods:

Patient Population:

A prospective hospital based randomized study was conducted over a period of 18 months in the Department of Radiotherapy, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi.

Thirty patients of histologically proven stage III–IV-A oropharyngeal, laryngeal & hypopharyngeal carcinoma were randomised in each arm using random number tables.

Patients had ECOG PS ≤ 2 and adequate bone marrow function (haemoglobin >10 gm/dl, absolute neutrophil count >1500 /cumm, platelets $>100,000$ /cumm), hepatic and renal function (calculated creatinine clearance >60 mL/min). Exclusion criteria included stage IV-B disease, previous treatment with RT or chemotherapy, any prior or synchronous malignancy, hypersensitivity to platinum agents or serious medical disease. Patients whose lymph nodes were large enough or extending behind the spinal cord where it would be difficult to spare the cord were not included in the study. Written informed consent was taken from all patients before the start of therapy and the study was carried out after the protocol was approved by the institution's ethics review board.

Treatment:

30 patients were randomly allotted in two arms:-

Arm A(control) received radiation as a single daily fraction of 2 Gy /day, 5 days a week to a total dose of 44 Gy/22 #/ 4½ weeks, followed by boost of 22 Gy/ 11 #/ 2 weeks to the primary with spinal cord shield, amounting to a total tumor dose of 66Gy/ 33#/ 6½ weeks.

Arm B (study) received a total dose of 66 Gy as follows -

Phase 1 - 44 Gy/22 # over 4½ weeks

Phase 2a- 12Gy/8 # over 1½ weeks with spinal cord shield with concomitant boost (at least after 6 hours) to the primary as phase 2b - 10 Gy/8 # over 1½ weeks.

Cisplatin was given weekly at a dose of 30 mg/m² intravenously in saline drip with adequate premedication and hydration. Blood counts and Creatinine levels were checked before every cisplatin administration.

Evaluation of Response And Toxicity:

Evaluation was done at 6 weeks and thereafter 12 and 24 weeks of completion of radiotherapy. Assessment of response to treatment was done by using the New Response Evaluation Criteria in Solid Tumors: Revised RECIST guideline (version 1.1).

The toxicities were evaluated and compared by using Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010) and Acute Radiation Morbidity Scoring Criteria -Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) group.

The results were subjected to appropriate statistical analysis. Continuous data was analyzed by analysis of variance in normal distribution. Chi square test or fishers test was used for categorical variables. A significance level of .05 was used.

Results:

The present study included 60 patients of loco-regionally advanced head and neck cancers .57 patients completed the treatment whereas 3 patients left the treatment and were not including in the analysis. Patients were well balanced between the two groups in terms of baseline characteristics (Table 1).

Demographic characteristics	ARM A CONTROL	ARM B STUDY
Median Age(yrs)	57.5	52
Sex ratio (M:F)	6.25:1	8.33:1

Site (%) (HPX:OPX:LX)	24:55:21	14:68:18
Histology(SCC) WD:MD:PD:NOS	21:38:10:31	18:46:11:25
T stage (%) (T1:T2:T3:T4)	0:24:48:28	0:18:54:28
Nodal stage (%) (N0:N1:N2:N3)	7:45:48:0	7:36:57:0
Stage distribution (%) (III:IV)	41:59	29:71

Table No.1 Showing baseline characteristics

Most of the patients in both the arms had a good performance status. 79.31% of the patients in arm A and 71.42% of patients in arm B were chronic smokers. The majority of patients presented with pain (localized and/or referred) as the predominant symptom (41.37% Vs 42.10%) followed by difficulty in swallowing and hoarseness of voice.

Treatment interruption

In our study, 82.75% (n=24) of the patients received complete 6 cycles of weekly chemotherapy in control arm as compared to 78.57% (n=22) of patients in study arm. Only one patient in control arm and two patients in study arm could not complete planned radiotherapy. Remaining all the patients received full dose radiotherapy with minor variations. However, Radiotherapy treatment interruptions were more in study arm as compared to control arm [42.85% vs. 27.58%]. Number of interrupted days varied from 3 days to 13 treatment days.

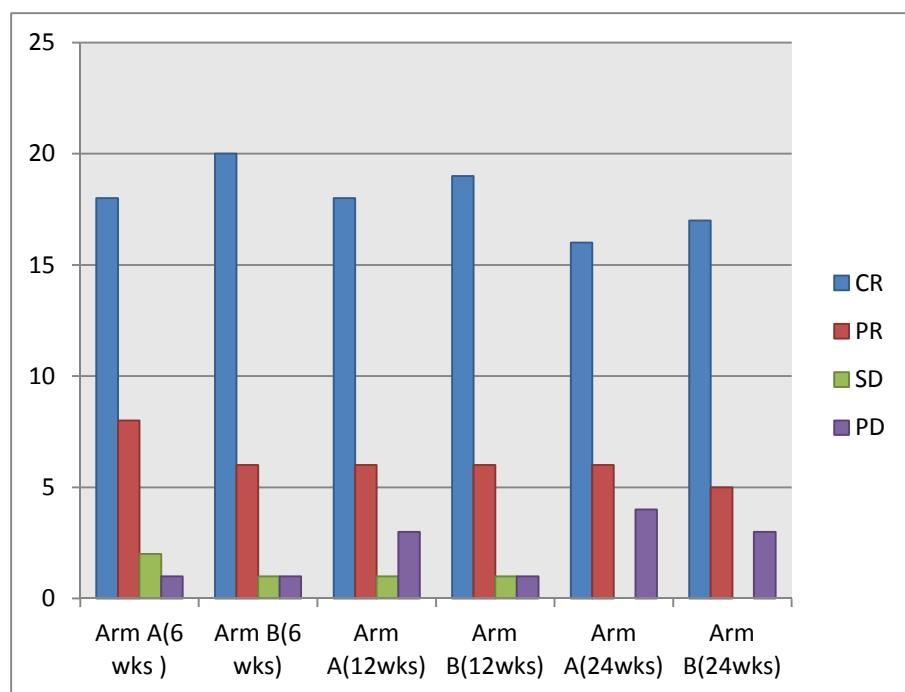
Treatment interruption (in days)	Control Arm N=29	Study Arm N=28	P VALUE
No	21	16	.2744 (NS)
<1 week	6	7	.7598 (NS)
1-2 weeks	2	5	.2529 (NS)

Table No.2 Showing The Radiotherapy Interruption

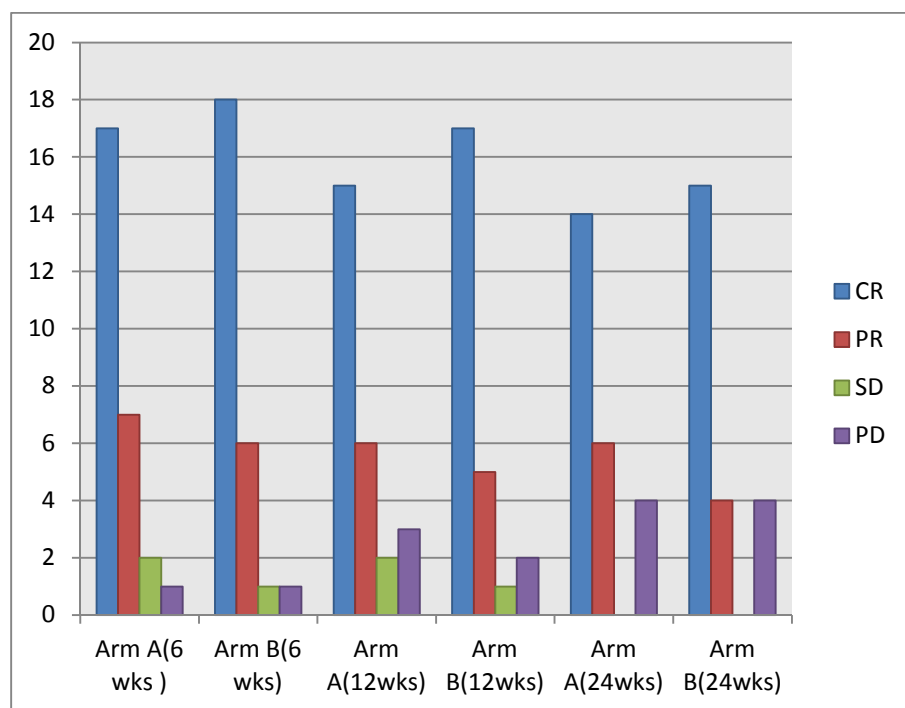
Response assessment:

In the present study the first response assessment was done at six weeks after completion of the treatment. The median follow-up is 11 months for control arm and 10.6 months for study arm patients. We identified CR at primary site in 62.06% of patients treated with standard fractionation while 71% patients in study arm achieved CR at six weeks after completion (p=.5765). Furthermore, 63% in control arm and 69%% patients in study arm achieved complete response at nodal site. Second and third follow-up was done at 12 and 24 weeks. At 12 weeks follow up, 64%Vs 70% patients showed CR at primary and 57%Vs 68% at nodal site in control and study group, respectively. At 24 weeks follow up, Primary and Nodal CR was seen in 61.53% and 58% in control arm compared to 68% and 65% in the study arm respectively.

Stage III disease showed a better complete response rate in both control arm and study arm compared to stage IVA disease.



Graph 1 Comparing Response Rates At Primary



Graph 2 Comparing Response Rates At Nodal Sites

Toxicity analysis:

Gastrointestinal, neurological and renal toxicity appeared to be comparable in both arms. Hematological toxicity (grade 3 anemia and neutropenia) was more in the study arm than control arm (7.14% Vs 0% and 14.28% Vs 0%). Tube feeding was performed in 31.03% of the patients in control arm as compared to 50% in study arm. Moreover, nine (31.03%) patients in control arm required intravenous fluid support as compared to fifteen (53.57%) in study arm. Most common acute toxicity observed in the present study was grade 3 mucositis which was seen in 71.42% of patients in the study arm and 27.58% of patients in the control arm ($p=.0014$, SS). Grade 3 skin reactions (32.14% Vs 20.68%) and grade 4 skin reactions (10.71% Vs 3.57%) were noted in study and control arms respectively. Incidence of Grade 3 dysphagia requiring supportive treatment (53.57% Vs 34.48%) and grade 3 xerostomia (35.71% Vs 20.68%, $p=.2483$) was higher in patients in study arm. Late toxicity was assessed at 24 weeks follow up. There was no statistically significant difference between the two arms with respect to late toxicity.

Discussion:

The treatment of loco-regionally advanced head and neck cancers has undergone a paradigm shift over the past three decades, with management strategies changing from surgery or radiation therapy as single modality to combined modality treatment.¹²⁻¹³ There has been intensive clinical research aimed at improving locoregional tumor control in advanced head and neck carcinomas by using altered radiation fractionation regimen. The two groups of biologically sound modified fractionation regimens that have been extensively studied are hyperfractionation and accelerated fractionation.¹⁴ The rationale for altered fractionation schedules in radiotherapy is based on a difference in tumor and normal tissue cellular repair and repopulation kinetics. A phase III trial RTOG 90-03, revealed that both the hyperfractionated regimen and accelerated fractionation by concomitant boost regimen yielded significantly better locoregional control than standard fractionation in patients with advanced head and neck carcinoma.¹⁵ Both concomitant chemotherapy and altered fractionation radiotherapy (RT) have been shown to improve outcomes for patients with loco-regionally advanced head and neck squamous cell carcinomas. However, both strategies also increase acute toxicity, and it is questionable whether the 2 can be safely combined. Thus the present study was conducted to document the feasibility of a concomitant boost regimen with weekly cisplatin delivered concurrently, in advanced head and neck cancers seen in the Indian subcontinent. Around 80% patients in control arm and 71% in study arm were chronic smokers. A review of studies conducted between 1994 and 2001 indicates a strong causal relationship between smoking and cancer of the oral cavity. Smoking is identified as an independent risk factor in 80% to 90% of patients who present with cancer of the oral cavity.¹⁶ Most of the patients presented in stage IVA, with similar distribution in both the arms. Overall, study arm had more loco-regionally advanced disease. Radiotherapy treatment interruptions were more in study arm as compared to control arm [42.85% vs. 27.58%]. Number of interrupted days varied from 3 days to 13 treatment days. The cause of this difference can be explained with grade 3–4 mucositis which affected 78.57% of patients and hematological toxicity in patients receiving concomitant boost radiotherapy with weekly cisplatin. Medina et al¹⁷ observed that 95% patients received full dose chemotherapy and radiotherapy, with minor variations. Treatment interruption was seen in 14 patients with a median delay of 6 days (range 3-10 days). We identified complete response at primary site in 62.06% of patients treated with standard fractionation with weekly cisplatin, while 71% patients in study arm achieved complete response at six weeks after completion. Furthermore, 63% in control arm and 69% patients in study arm achieved complete response at nodal site. RTOG 99-14 TRIAL showed a complete response of 83% and partial response of 13% at four weeks after the completion of the treatment.²⁰ 88% patients achieved overall response with 66% showing complete and 22% with partial response in a study by Medina et al¹⁷. Similar results were also shown in a phase II study at one month after treatment completion with 67% and 61% complete response at primary and nodal site, respectively.¹⁸

Thus our results were in concordance with literature.

Tube feeding was performed in 31.03% of the patients of control arm as compared to 50% in study arm. Moreover, nine (31.03%) patients of control arm patients required intravenous fluid support as compared to fifteen (53.57%) in study arm.

Heather et al¹⁹ observed ryles tube feeding in 54% patients-16% before and 38% during treatment. Similarly in a phase II Indian study¹⁸ around 26% patients were put on tube feeding with average duration of 19.3 days.

Most common acute toxicity observed in present study was grade 3 mucositis which was seen in 71.42% of patients in the study arm and 27.58% of patients in the control arm ($p=0.0014$, SS). Medina et al¹⁷ also noted mucositis as a common acute toxicity which reached grade 3 in 85% of patients treated with weekly cisplatin. Shaleen kumar et al¹⁸ in a phase II trial observed grade 3 and 4 mucositis was seen in 73 and 6 % patients, respectively. In RTOG trial 9914, 50% patients showed grade 3 and 3% patients showed grade IV reactions.²⁰

Grade 3 skin reactions (32.14% Vs 20.68%) and grade 4 skin reactions (10.71% Vs 3.57%) noted in study and control arms respectively, were also similar to those found in the study by RTOG phase II trial 99-14²⁰. Vivek et al²¹ showed 41.66% grade 3 skin reaction in the concomitant boost arm. 17% patients developed grade 3 skin reactions in the study done by Medina et al.¹⁷

Grade 2 dysphagia was higher in control arm (55% Vs 42.85%) but grade 3 dysphagia requiring supportive treatment was higher in study arm (53.57% Vs 34.48%). Incidence of grade 3 dysphagia in phase II trial RTOG 99-14 and study by Medina et al was 58% and 50% respectively.

Initial nodal involvement and stage showed association with treatment outcome with lower nodal status and stage showing more complete responses. Given these findings we believe that concomitant boost accelerated radiation therapy plus concurrent weekly cisplatin is a feasible schedule in patients with locally advanced unresectable head and neck carcinoma, with acceptable toxicity. The compliance to therapy is high, and the loco-regional control achieved compares favourably with concurrent chemo-radiation by conventional fractionation with weekly cisplatin.

However with the small number of sample size, inherent bias of single institutional trial and short duration of follow up the exact evaluation of local control and toxicity could not be achieved. So, further evaluation and randomized trials are needed to compare the results in these two arms.

Conclusion:

Although the findings in our study lead us to believe that concomitant boost chemo-radiation is a safe and effective treatment regimen with comparable results, the results need to be viewed with cautious optimism. Our study offers the prospect of the possibility of customizing the different schedules of concomitant chemo-radiation according to the patient profile keeping in mind the limited resources, time constraints, availability of support systems without affecting the treatment outcomes grossly.

References:

1. Argiris A, Karamouzis MV, Raben D, Ferris RL. **Head and neck cancer.** *Lancet* 2008;**371**(9625):1695-1709.
2. Macfarlane GJ, et al.: **Alcohol, tobacco, diet and the risk of oral cancer: a pooled analysis of three case-control studies.** *Eur J Cancer B Oral Oncol* 1995, **31B** (3):181-7.
3. Cooper JS, Porter K, Mallin K, et al. **National Cancer Database report on cancer of the head and neck: 10-year update.** *Head Neck* 2009;**31**(6):748-758.
4. Wang CC, Blitzer PH, Suit HD: **Twice-a radiation therapy for cancer of the head and neck.** *Cancer* **55**:2100-2104, 1985.
5. Cox JD, Pajak TF, Marcial VA, et al: **Dose response for local control with hyperfractionated radiation therapy in advanced carcinomas of the upper aerodigestive tracts: Preliminary report of Radiation Therapy Oncology Group protocol 83-13.** *Int J Radiat Oncol Biol Phys* 1990 **18**:515-521.
6. Ang KK, Peters LJ, Weber RS, et al: **Concomitant boost radiotherapy schedule in the treatment of carcinoma of the oropharynx and nasopharynx.** *Int J Radiat Oncol Biol Phys* 1990 **19**:1339-1345.

7. Mendenhall WM, Riggs CE, Amdur RJ, et al. **Altered fractionation and/or adjuvant chemotherapy in definitive irradiation of squamous cell carcinoma of the head and neck.** *Laryngoscope* 2003; **113**:546-551.
8. Al-Sarraf M, Pajak TF, Marcial VA, et al: **Concurrent radiotherapy and chemotherapy with cisplatin in inoperable squamous cell carcinoma of the head and neck. An RTOG study.** *Cancer* **59**:259-265, 1987
9. Tobias JS, Smith BJ, Blackman G, et al: **Concurrent daily cisplatin and radiotherapy in locally advanced squamous carcinoma of the head and neck and bronchus.** *Radiotherapy Oncol* **9**:263-268, 1987
10. Jeremic B, Shibamoto Y, Stanisavljevic B, et al: **Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: A prospective randomized trial.** *Radiother Oncol* **43**:29-37, 1997.
11. Nguyen LN, Ang KK: **Radiotherapy for cancer of the head and neck: Altered fractionation regimens.** *Lancet* **3**:693-701, 2002
12. Pignon JP, le Maitre A, Bourhis J, MACH-NC Collaborative Group: **Meta-analyses of Chemotherapy in Head and Neck Cancer (MACH-NC).** *Int J Radiat Oncol Biol Phys* 2007, **69**(2 suppl):S112-114
13. Brizel DM, Albers ME, Fisher SR, et al: **Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer.** *N Engl J Med* 1998, **338**:1798-1804,
14. Bernier J, Bentzen SM: **Altered fractionation and combined radio-chemotherapy approaches: Pioneering new opportunities in head and neck oncology.** *Eur J Cancer* **39**:560-571, 2003
15. Fu KK, Pajak TF, Trotti A, et al: **A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: First report of RTOG 9003.** *Int J Radiat Oncol Biol Phys* **48**:7-16, 2000
16. Sturgis EM, Cinciripini PM. **Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers.** *Cancer* 2007;**110**(7):1429-1435.
17. Jose´ Antonio Medinaa, Antonio Ruedab, Antonio Sacchetti de Pasosc, Jorge Contrerasd, **Phase II study of concomitant boost radiation plus concurrent weekly cisplatin for locally unresectable head and neck carcinomas** *Radiotherapy and Oncology* **79** (2006) 34–38.
18. Shaleen Kumar,Manish Pandey , Punita Lal **boost radiotherapy with concurrent weekly cisplatin in advanced head and neck cancers: a phase II trial** May 2005.
19. Heather E. Newlin MD1, Robert J. Amdur Jessica M. Kirwan ,William M. Mendenhall MD1 **Concomitant weekly cisplatin and altered fractionation radiotherapy in locally advanced head and neck cancer:** 19 AUG 2010.**21**:193-6
20. K. Kian Ang, Jonathan Harris, Adam S. Garden Andy Trotti, Randal S. Weber **RTOG (99-14)Concomitant Boost Radiation Plus Concurrent Cisplatin for Advanced Head and Neck Carcinomas: Radiation Therapy Oncology Group Phase II Trial** 99-14: 21-231
21. Vivek RS, Baludavid M, Mohanram R, Chitra, Amanullah, Vijayalakshmi, Bala, Kalaiyarasi, Saravanan. **Concurrent chemo-irradiation using accelerated concomitant boost radiation therapy in loco-regionally advanced head and neck squamous cell carcinomas.** *J Can Res Ther* 2006; **2**:90-6