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Is Accelerated Radiation Therapy an Answer where Concurrent Chemoradiation is not Feasible for the Management of Locally Advanced Head and Neck Cancers? A Contribution to the Controvert

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Abstract

Background: Head and neck carcinomas are still challenging in the present era. This prospective study has been done to compare standard concurrent chemoradiation with modest accelerated radiotherapy.

Material and Methods: Prospective study was done on 150 patients who were, histopathologically proven locally advanced squamous cell carcinoma of the head and neck region presented to PGIMS, Rohtak. They were randomly allotted altered fractionation i.e. 66Gy/33 fractions/5.3 weeks/6 fractions per week (group I) or conventional fractionation radiotherapy plus concomitant chemotherapy i.e. 66Gy/33 fractions/6.3 weeks/5 fractions per week) with weekly injection cisplatin 30 mg/m^2 (group II). The end points were tumor response, acute and late toxicities and Overall Survival (OS) at 24 months.

Results: All the patients were able to complete the treatment in both the groups. Median follow up was 24 months. Complete response at the end of 24 months was observed in 34 (45.33%) and 36 patients (48%) in group I and group II respectively (p-value =0.744). Toxicity profile didn't show any statistically significant difference in either group except renal toxicity and weight loss. Slightly higher incidence of acute toxicity was seen in group I patients without any statistical significance.

Conclusion: The modest accelerated radiotherapy fractionation with reduced overall time in comparison to conventional chemoradiation is a reasonable option for locally advanced head and neck cancers while avoiding the side effects related to chemotherapy. However large randomized data is required for incorporation into guidelines.

Keywords: Head and neck cancer; Accelerated radiotherapy; Chemotherapy; Cisplatin; Altered fractionation

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Introduction

Head and neck cancers are on increasing trend worldwide with annual incidence of 834,860 cases in 2018. It is the most common cancer amongst males and fourth most common cancer amongst females in India [1]. But there is disproportionately in overall burden globally with 57.5% of global head and neck cancer cases occurring in Asia especially in India [2]. Tobacco smoking is the commonest known etiological factor [3]. However in India bidi and hukka smoking are prevalent forms and mostly not quantified properly and Western literature should be extrapolated with caution. Pathogenesis of alcohol induced cancer is synergistic with cigarette smoking and also with malnutrition, vitamin deficiency etc. Poor nutritional status and inadequate vitamin intake are associated with higher risk of head and neck cancer. All these risk factors along with variable demographic profile, food habits and living style accounts for high incidence of head and neck cancers in Asian region which require extensive and coordinated research.

Approximately 70% to 80% of these head and neck cancer patients are diagnosed with locally advanced disease [4]. Oncological treatment has been advanced promisingly over the past decades. Delivering a total dose of 66 Gy to 70 Gy with 1.8 Gy to 2 Gy/fraction for five days in a week

over 6-7 weeks is considered as standard fractionation schedule with concurrent chemotherapy in locally advanced cases [5,6]. Even with this treatment survival rate are 37% to 73% and one of the major obstacle for cure of head and cancers is tumor cell repopulation during fourth to fifth week of conventional fractionation regimen [7,8]. Compliance, cost and treatment tolerance are the other concerns. Various types of altered fractionation schedules have been attempted to improve local control and survival in these patients. One type of altered fractionation is accelerated fractionation, which aims at shortening the overall treatment time to counteract tumor cell repopulation.

A recently published update of Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) has shown the benefit of altered fractionation over conventional fractionation but failed to show the benefit over concomitant chemo radiation. Overall survival was significantly worse with altered fractionation radiotherapy compared with concomitant chemoradiotherapy (HR 1.22, 1.05-1.42; p=0.0098), with absolute differences at 5 years of -5.8%. But the trials related to direct comparison for altered fractionation over concomitant chemo radiation were only 5 with much accelerated radiotherapy accounts for most of the data. Further research is thus needed in this context [9].

The present study was planned to evaluate the feasibility, efficacy and toxicity of modestly accelerated radiotherapy in the treatment of locally advanced head and neck cancers in a single institute. Since conventionally fractionated chemo-radiation is the standard recommended treatment for locally advanced head and neck cancers, it has been planned to compare accelerated radiation therapy with conventional fractionated chemoradiation.

Materials and Methods

This prospective study was conducted on 150 patients who were, histopathologically proven patients of locally advanced squamous cell carcinoma of the head and neck region, previously untreated, who attended the Department of Radiotherapy, Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak. The study is approved by institutional ethical committee.

The patients were randomly divided in two groups of 75 patients each by draw of lots. Group I patients' were given six fractions per week of radiation therapy (66 Gy/33 fractions/6 fractions per week for an overall period of 5.3 weeks). Patients of group II were given five fractions per week of radiation therapy (66Gy/33 fractions/5 fractions per week for an overall period of 6.3 weeks) concomitant with weekly cisplatin 30 mg/m^2.

Inclusion criterion were histopathologically proven cases of squamous cell carcinoma of head and neck region of stage III/IV-A/IV-B (The American Joint Committee on Cancer 7th edition) with good performance status (Karnofsky Performance Status ≥ 70) and normal biochemical profile [10,11]. The patients with distant metastases, prior radiation, surgery or chemotherapy for this disease, poor general condition with KPS <70 and/or pregnant or lactating females were excluded from the study.

Hematological, liver and renal toxicity and nausea/vomiting toxicity observed during treatment as per World Health Organization (WHO) criteria [10]. Skin and Mucosal reactions were observed as per Radiation Therapy Oncology Group (RTOG) criteria and weight loss was assessed at the beginning of treatment, thereafter weekly

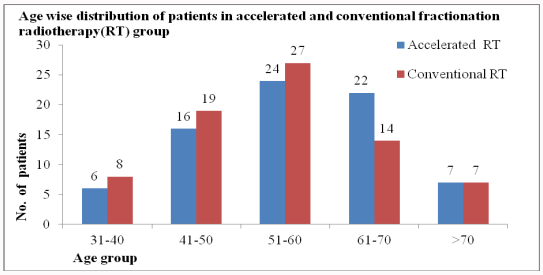

Figure 1: Age wise distribution of patients in group I (accelerated fractionation) and group II (conventional fractionation radiotherapy plus concomitant chemotherapy).

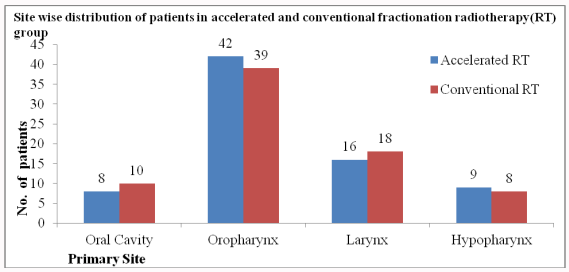

Figure 2: Site wise distribution of patients in group I (accelerated fractionation) and group II (conventional fractionation radiotherapy plus concomitant chemotherapy).

Table 1: Tumor response at 6 weeks of completion of treatment (WHO response criteria).

	No. of Patients (%)		p Value
Tumor response	Group I (n=75)	Group II (n=75)	
Complete Response (CR)	58 (77.33)	55 (73.33)	0.571
Partial Response (PR)	12 (16)	16 (21.33)	0.404
No Response (NR)	3 (4)	2 (2.67)	0.651
Progressive Disease (PD)	1 (1.33)	1 (1.33)	1
Lost to follow up	1 (1.33)	1 (1.33)	1

during treatment and at the completion of treatment as per South West Oncology Group (SWOG) criteria. Late radiation toxicity (graded according to RTOG criteria) was noted in terms of skin toxicity, subcutaneous toxicity, mucous membrane toxicity and salivary gland toxicity.

All the patients were treated on Telecobalt machine in supine position by bilateral parallel opposed fields to face and neck as per departmental protocol and dose was prescribed to the mid plane at the central axis. The spinal cord sparing fields were planned after 44 Gy.

After treatment all the patients were followed up every fortnightly for one month and then, followed up every three months till 2 years. WHO criteria was used to assess tumor response.

Statistical Analysis

Data was analyzed using SPSS (Statistical package for social sciences) version 16.0 for Windows. Quantitative data was presented as Mean and Standard deviation. For qualitative data, Chi square test was used. For statistical significance, p value less than 0.05 was taken as point of statistical significance.

Table 2: Disease status at 6th, 12th and 24th month of follow up (WHO response criteria).

Disease status at follow up	Group I (n=75)			Group II (n=75)		
	No of patients (%)			No of patients (%)		
	6th month	12th month	24th month	6th month	12th month	24th month
No evidence of disease	46 (61.33)	37 (49.33)	34 (45.33)	43 (57.33)	39 (52)	36 (48)
Residual disease	15 (20)	13 (17.33)	12 (16)	12 (16)	11 (14.67)	10 (13.33)
Recurrent disease	6 (8)	11 (14.67)	14 (18.67)	9 (12)	11 (14.67)	14 (18.67)
Lost to follow up	7 (9.33)	12 (16)	13 (17.33)	11 (14.67)	14 (18.67)	15 (20)

Results

150 patients were included in the study with comparable demographic parameters; however the difference was small and insignificant. Mean age (± Standard deviation) was 57.73 ± 9.73 and 54.49 ± 11.03 years in group I and group II respectively. Age wise distribution is shown in (Figure 1). 88% and 85.3% patients were from rural population in group I and group II respectively thus majority of patients belong to rural population. Male population was dominating in both groups with 65 males in group I and 64 males in group II. Although majority of patients were smokers in both the groups with slightly high number i.e. 70 in group I as compared to 68 in group II. Similar variation was reported in alcohol intake with 48 *vs.* 53 in group I and II respectively. Karnofsky Performance Status was reported between 70 to 80 in all the patients in either group.

In both groups, pain throat followed by difficulty in swallowing was the chief presenting complaint. In both the groups, oropharynx was the most common site of presentation followed by larynx (Figure 2). The most common histopathological type was moderately differentiated squamous cell carcinoma. Overall AJCC stage III patients were 58.67% and 54.67% patients in Group I and II respectively.

Grade 3 mucositis was observed in 21 (28%) patients in group I, and 15 (20%) patients in group II, the difference were not statistically significant. Grade 1 mucositis was noted in 22 patients (29.33%) in group I and 24 patients (29.33%) in group II and grade 2 mucositis in 32 (42.67%) and 36 (48%) patients in group I and group II respectively. Treatment was interrupted in five patients for 1 week due to grade 3 mucosal reactions in group I while three patients had treatment interruption in group II. Grade 4 mucositis was not seen in either of the group.

Grade 2 skin reactions were noticed in 31 (41.33%) patients of group I and 24 (32%) patients of group II. 6(8%) patients in group I and 4 (5.33%) patients in group II developed grade 3 skin reactions. Grade 4 skin reactions were not seen in any of the patients (Figure 3). There was no statistically significant difference at all comparative points.

Maximum toxicity observed pertaining to liver enzymes was grade 2 (3 (4%) patients in group II in Serum Glutamic Pyruvic Transaminase (SGPT)). Grade 1 renal toxicity was observed in 2 (2.6%) patients in group I and 15(20%) patients of group II, difference was statistically significant (p value 0.0008). No grade 2 or more renal toxicity was observed in either group.

Grade 1 hematological toxicity pertaining to hemoglobin was observed in 13 (17.33%) patients of group I in comparison to 19 (25.33%) patients of group II. No patient had Grade 2 in group I in comparison to 4 (5.53%) patients in group II but the difference was not statistically significant (p value 0.039). 6(8%) patients in group I and 10 (13.33%) patients in group II developed grade 1 decrease in total leukocyte count (p value 0.291). No Grade 2/3/4 hematological toxicity in terms of total leukocyte count was noticed in either group.

Grade 1 and grade 2 weight loss was observed in 50 (66.67%) and 10 (13.33%) *vs.* 39 (52%) and 24 (32%) patients in group I and II respectively with statistically significant difference (p value 0.014). No patient in either group experienced grade 3/4 weight loss. In most of the patients, nausea/vomiting leading to inadequate oral intake appeared to be the factors for weight loss. None of patients in group I experienced grade 3/grade 4 nausea or vomiting. More nausea or vomiting was observed in group II i.e. 47 patients due to use of concomitant chemotherapy in comparison to only 29 patients in group I. In group II, highest level of nausea/vomiting was grade 3 observed in 6 patients and grade 2 in 22 and grade 1 in 19 patients. However 46 patients in group I had no such toxicity in comparison to 28 patients in group II (p=0.0034).

There was no grade 3 and 4 late toxicity in any groups, except for 6 (8%) patient from group I and 3 (4%) patients from group II developed grade 2 late subcutaneous toxicity. No statistically significant difference was found between the two groups in terms of late toxicity.

At 6 weeks post treatment, 77.33% patients of group I and 73.33% patients of group II had Complete Response (CR), whereas Partial Response (PR) was seen in 16% & 21.33% each in group I & II respectively (Table 1). One patient in each group lost to follow up at the end of 6 weeks.

There was no evidence of disease at 6th month follow up in 46 patients of Group I and 43 patients of Group II. Seven patients in group I and 11 patients in group II didn't come for follow-up at the end of 6 months and this number increased to 13 in group I and 15 in group II at 24 months. At the end of 24 months no evidence of disease was seen in 34 patients *vs.* 36 patients in group I and II respectively with no statistically significant difference (p-value =0.744) (Table 2).

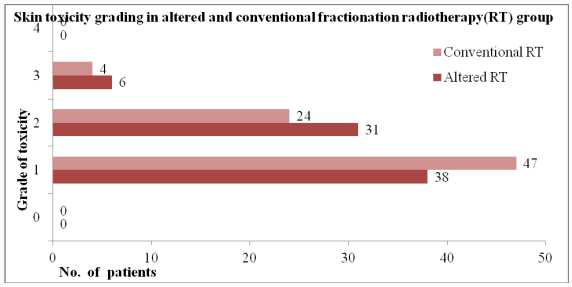

Figure 3: Skin reactions observed during treatment in group I (accelerated fractionation) and group II (conventional fractionation radiotherapy plus concomitant chemotherapy) in head and neck cancer patients.

Table 3: Summary of trials comparing altered fractionation versus conventional fractionation radiotherapy (± chemotherapy) in head and neck malignancies (#-fraction).

Study (year)	No of patients	Altered fractionation arm		Conventional arm		
		Regimen	Survival	Regimen	Survival	
Ghosh Laskar S et al. [22]	50 each	Accelerated normo fractionated RT:2Gy/#, 6#s/wk to a dose of 66-70Gy in 33-35# over 5.5-6 wks	44% at 2-years	RT: 66-70Gy/ 33-35#/6.5-7 wks Cisplatin @ 30mg/ m^2 weekly x 6-7cycles throughout RT	58% at 2-yrs	p=0.35
Overguard et al. [21]	Altered fractionation-418 Conventional fractionation 413	6#/week to a total dose of 66-70Gy in 33-35 fractions	OS-35% at 5 years LRC-42%at 5 years	5 #/week to a total dose of 66-70 Gy in 33-35 fractions	OS-28% at 5 years LRC-30% at 5 years	p=0.07 (OS) p=0·004 (LRC)
Overguard et al. [18] (DAHANCA 6&7)	Altered fractionation-750 Conventional fractionation-726	6#/week to a total dose of 66-68Gy in 33-34 fractions	Overall 5-year LRC 70% DFS 73% No OS benefit	5 #/week to a total dose of 66-68Gy in 33-34 fractions	Overall 5year LRC 60% DFS 66%	p=0.0005 p=0.01 (DFS)
Hiliniak et al. [23]	Altered fractionation-196 Conventional fractionation- 199	66Gy given in 33 fractions over 38 days (2 fractions every Thursday)	LRC in 12, 24 and 36 months were 86, 82, 81%, respectively	66Gy given in 33 fractions over 45 days	LRC in 12, 24 and 36 months were 83, 78, 76%	p=0.33

Two patients expired in group I due to unrelated cause, one at the end of 15 days of treatment and another one after 6 months of treatment. No death was reported in group II.

We also did subgroup analysis by assessing response in elderly patients. 61 years and above were included in this analysis with 29 patients in group I and 21 patients in group II (Figure 1). There were 12 out of 29 patients (41.38%) in accelerated group *vs.* 9 out of 21 patients (42.86%) in conventional chemoradiation group having no evidence of disease at the end of 24 months.

Discussion

Head and neck cancers are most common cancers among males in India and 2nd most common in the combined population [1]. Multiple risk factors have been implicated in their causation around the world but there is lot of geographic variation in risk factors and incidence. Alcohol and tobacco are trigger factors for head and neck cancers, which together probably account for three-quarters of cases [12]. There is increase in relative risk by 5 to 25 folds for the smokers. Similar picture is seen in the present study as >90% patients are smokers redefining the role as well established risk factor. Mean age was 57.73 and 54.49 years in group I and group II respectively. This is in accordance to previous literature suggesting the peak age incidence for head and neck carcinoma is between fifth and sixth decade of life [13-15]. Majority of the patient are males comprising 86.67% in group I and 85.34% in group II.

The state of the art regarding radiation dose fractionation has evolved from conventional fractionation to hyper-fractionation and accelerated fractionation. They regarded as accelerated repopulation was regarded as cause of treatment failure. There is 7% to 10% improvement in loco-regional control with these altered strategies as compared to conventional Radiation treatment [16-18].

Accelerated treatment strategy aims to deliver the same total dose over a shorter overall treatment time. This prospective comparative study was conducted to compare the local control and toxicity of altered fractionated radiotherapy (six fractions per week) i.e. group I *vs.* concomitant conventionally fractionated radiotherapy with chemotherapy (five fractions per week with weekly cisplatin 30 mg/m^2) i.e. group II, in 150 patients of locally advanced head and neck carcinomas. Although there was higher incidence of hematological, renal, hepatic toxicities and nausea/vomiting noted in group II in comparison to group I but only difference in renal toxicity and weight loss was statistically significant. But renal toxicity noted was grade 1 only. There was statistically insignificant higher incidence of acute mucosal toxicity noted in group I in comparison to group II.

According to literature, the most frequently seen side effect of radiation therapy in patients with head and neck cancer is radiation dermatitis that occurs in approximately 90% of patients [19]. Majumder et al. [20] observed grade 2 and grade 3 skin toxicity in 53% and 47% patients respectively. However lower rates were seen in the patients of the present study with grade II skin reactions noticed in 31 (41.33%) patients of group I and 24 (32%) patients of group II with no statistical difference. 6 (8%) patients in group I and 4 (5.33%) patients in group II developed grade 3 skin reactions. However compliance was not affected. Overall confluent mucositis was noted in 21 (28%) patients in the accelerated group and 15 (20%) patients in the conventional chemoradiation group. This is slightly higher than study by Overguard et al. [21] where 45 (10%) patients in the accelerated group and 22 (5%) patients in the conventional radiation alone group (Hazard Ratio 2.15) suffered confluent mucositis. However, compliance is affected more in accelerated group with 5 patients' *vs.* 3 patients in conventional chemoradiation group due to grade 3 mucositis leading to treatment prolongation by 3 days to 1 week. This difference may be due to oral hygiene maintenance differences.

One of the largest trials on altered fractionation by Overguard et al. [21] also compared six fractions with five fractions per week conventional radiotherapy in the management of squamous cell carcinoma of head and neck and assessed the tumor response [18]. They did multicentre, controlled, randomized trial over 5 years of 1476 eligible patients treated with primary radiotherapy alone. Overall 5-year locoregional control rates were 70% and 60% for the six fraction and five-fraction groups, respectively (p=0.0005). Acute morbidity was significantly more frequent with six than with five fractions, but was transient. However in the present study the locoregional control was 45.33% at the end of 24 months in altered fractionation group *vs.* 48% in concomitant chemoradiation group with similar morbidity profile. Although more number of patients showed complete response in group I at 6 weeks post treatment i.e. accelerated fractionation group but difference was small and statistically insignificant.

Number of cases with residual disease was more in group I in comparison to recurrent disease. However the difference in terms of residual and recurrent disease was also insignificant even at the end of 24 months.

Another large study by Overguard et al. [21] overcoming the barriers of geographical variation from centers all over the world including Asia, Africa, Europe and South America, reported 5-year actuarial rate of locoregional control was 42% in the accelerated group *vs.* 30% in the conventional group (Hazard Ratio (HR) 0.63, 95% CI 0.49-0.83; p=0.004). On extrapolation of this study we found around 50% *vs.* 60% locoregional control at 6 months with conventional and altered fractionation respectively. However present study needs extended follow up for a better comparison of the results. They noted confluent mucositis in 45 patients out of 418 patients (10.77%) in the accelerated group *vs.* 22 patients out of 413 patients (5.33%) in the conventional group, which was lesser as compared to present study. Table 3 summarizes the trials comparing altered fractionation *vs.* conventional fractionation radiotherapy (± chemotherapy) [22,23].

There is also concern for elderly patients with regard to treatment toxicity especially chemotherapy leading to deterioration of quality of life. Figure 1 shows 50 out of 150 patients were >60 years of age group (33.33%) in the present study and definitive treatment in them is a challenge as there is lot of heterogeneity in the geriatric population and probably require separate guidelines. In the present study there is approximately 4% difference at the end of six months in favor of accelerated radiotherapy thus emphasizing the value of avoidance of chemotherapy. Even in updated Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC), chemotherapy benefit in oldest age category have the hazard ratios close to 1 [24]. Thus chemotherapy can be avoided in such patients if accelerated fractionation proves itself at par with treatment outcome. However separate study on geriatric locally advanced head and neck carcinoma will clear the picture with regard to toxicity and treatment outcome.

Although there is proven role of concomitant chemoradiation in locally advanced head and neck carcinoma still in present era it is challenging to cure the disease and give appropriate quality of life to the patient. However altered fractionation is a good option in patients unwilling for concomitant chemotherapy or medical contraindications for chemotherapy with no compromise in treatment response.

Conclusion

Modest accelerated radiotherapy i.e. 6 fractions per week with reduced overall time is a reasonable option for locally advanced head and neck cancers while avoiding the side effects related to chemotherapy in a limited resource setup. Toxicity profile is also favorable in comparison to conventional concurrent chemoradiation treatment. To further explore and establish the role of accelerated radiation in management of locally advanced head and neck carcinoma, a larger study with more number of patients and longer follow up is needed.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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