

## Original Research

### Estimation of tumor regression parameters from dose response relationship in patients of head and neck cancer undergoing EBRT

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#### ABSTRACT:

**Background:** Head and neck carcinoma (HNC) is the sixth most common cancer worldwide. In India, it accounts for one fourth of male cancers and one tenth of female cancers. The present study estimated the tumor regression parameters from dose response relationship in patients of head and neck cancer undergoing EBRT to interpret the curvilinear L-Q curves as obtained from in vivo and in vitro studies. Also, these data were compared with  $\alpha/\beta$  ratio estimated by use of Fe plot method. **Materials & Methods:** 60 patients of locally advanced carcinoma of head and neck were enrolled. Local examination of oral cavity was done under aseptic conditions. Primary site of malignancy was inspected for site, size, shape, surface, borders, margins, base, infiltration to surrounding structures and any signs of inflammation. Patients were divided into 2 groups. Group A (Conventional): - This group consisted of randomly selected previously untreated 30 patients of squamous cell carcinoma of oropharynx. Group B (hyper fractionated): - This group consisted of randomly selected, previously untreated 30 patients of squamous cell carcinoma of oropharynx. **Results:** The mode ECOG was 1 in both the groups with 80% and 66.67% patients in the hyperfractionated and conventional arms, respectively having ECOG status 1. The Fe-plot drawn for the isoeffect doses of grade 1 mucosal reactions. X-axis depicts the dose per fraction of the treatment schedule and Y-axis shows the inverse of the mean isoeffect dose. The patients of the hyperfractionated arm developed grade 1 mucosal reaction at the mean isoeffect dose of 29.840Gy, while it was 27.667Gy for the conventional arm. The intercept on the y-axis (1/33.75) obtained by extrapolating the line joining the respective isodose lines corresponds to  $\alpha/\log_e S$  and the slope of the curve ( $3.235 \times 10^{-3}$ ) corresponds to  $\beta/\log_e S$ . **Conclusion:** The virtual  $\alpha/\beta$  represents the complex radiobiological phenomena taking place during fractionated radiotherapy. It incorporates the combined influence of cell loss, changing tumor kinetics, clonogen doubling, repair, reoxygenation, blood flow and clearance of the dead and necrotic tissue/debris and thus, could be more appropriate in clinical radiotherapy.

**Key words:** Conventional arms, Hyperfractionated, Squamous cell carcinoma.

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#### INTRODUCTION

Head and neck carcinoma (HNC) is the sixth most common cancer worldwide. In India, it accounts for one fourth of male cancers and one tenth of female cancers.<sup>1,2</sup> The incidence of HNC is about six times higher in India as compared to western countries probably due to oral consumption of tobacco in various forms, use of lime with betel nut and leaves and smoking. With changes in risk profile, both the incidence and the sub-site predilection may change.<sup>3</sup> Among females, the age-adjusted rates of India are the highest in the world. In India, oral cavity is the predominant site.<sup>4</sup> Globally, overall there continues to be increase of newly diagnosed oral cancers

particularly tongue cancers. In all countries, men are affected almost twice as often as women, probably due to their higher indulgence in risk factors such as alcohol and tobacco consumption.<sup>5</sup>

HNC includes malignancies arising from base of skull to the region of thoracic inlet. According to various studies, the prevalence of head and neck cancer with respect to total body malignancies ranges from 9.8% to 42.7%. The estimates for head & neck cancers in India for the year 2010 for males and females were 122,643 and 53,148, respectively.<sup>6</sup>

Radiation is an important modality in the treatment of head and neck carcinoma. There has been a great evolution in our basic biologic understanding of

ionizing radiation and its interaction with living tissue.<sup>7</sup> External beam radiotherapy (EBRT) being one of the important prognosticators of long term loco-regional disease control in head and neck cancer, patterns of tumor regression during the course of EBRT assumes special significance.<sup>8</sup> The present study estimated the tumor regression parameters from dose response relationship in patients of head and neck cancer undergoing EBRT to interpret the curvilinear L-Q curves as obtained from in vivo and in vitro studies. Also, these data were compared with  $\alpha/\beta$  ratio estimated by use of Fe plot method.

## MATERIALS & METHODS

In present study a total of 60 patients of locally advanced carcinoma of head and neck were enrolled for the study in the department of Radiotherapy, Acharya Tulsi Regional Cancer Treatment and Research Institute, Sardar Patel Medical College and associated group of hospitals, Bikaner. All the patients were histological proved cases of squamous cell carcinoma.

Complete history and general physical examination with an assessment of the patient's clinical performance status, and dental status was recorded. Clinical examination for evidence of lymphadenopathy and systemic examination to exclude any evidence of distant metastasis was done. Systemic examination of cardiovascular, respiratory, gastro intestinal and nervous system was also done.

Local examination of oral cavity was done under aseptic conditions. Primary site of malignancy was inspected for site, size, shape, surface, borders, margins, base, infiltration to surrounding structures and any signs of inflammation. All the findings of inspection were confirmed by palpation. Careful examination of lymphatic system of head & neck was performed for the level of lymph nodes (level 1 to 5) involved, number, size, consistency, mobility, and any sign of inflammation. All patients were staged according to the American Joint committee on cancer staging, 2011 staging system.

## RESULTS

**Table I ECOG Performance Status of the Patients**

S. No.	ECOG	Hyperfractionated Arm	Conventional Arm	$\chi^2$	P value
1.	<b>0</b>	4 (13.30%)	7 (23.34%)	2.751	0.097
2.	<b>1</b>	24 (80%)	20 (66.67%)	1.211	0.271
3.	<b>2</b>	2 (6.70%)	3 (10%)	0.652	0.419
4.	<b>Total</b>	30 (100%)	30 (100%)	-	-

Table I shows that the mode ECOG was 1 in both the groups with 80% and 66.67% patients in the hyperfractionated and conventional arms, respectively having ECOG status 1.

**Table II Age Distribution of the Patients**

S. No.	Age Group (years)	Hyperfractionated Arm	Conventional Arm	$\chi^2$	P value
1.	<b>31-40</b>	3 (10%)	2 (6.67%)	0.665	0.414
2.	<b>41-50</b>	11 (36.67%)	12 (40%)	0.145	0.703

Patients were divided into 2 groups. Group A (Conventional): - This group consisted of randomly selected previously untreated 30 patients of squamous cell carcinoma of oropharynx. These patients received injection cisplatin 40 mg/m<sup>2</sup> given intravenously 2 hours infusion six hours before radiation and repeated weekly for 6 cycles. All patients received 66 Gy concurrent radiation at the rate of 2 Gy/fraction, 1 fraction/day, 5 fractions/week, in 6-7 weeks by Theratron-780 E/780C & Bhabhatron-II telecobalt units by bilateral parallel opposed portals. Initial treatment fields included the primary tumor with adequate safe margins and primary nodal drainage region (whole neck). 44 Gy was delivered through these fields. Subsequently, field was reduced to spare spinal cord and the primary site was irradiated further 22 Gy to a total dose of 66 Gy.

Group B (hyper fractionated): - This group consisted of randomly selected, previously untreated 30 patients of squamous cell carcinoma of oropharynx. These patients were also given weekly injection cisplatin 40 mg/m<sup>2</sup>. It was given intravenously as a 2 hours infusion six hours before radiation and repeated weekly for 6 cycles. All patients were given 72 Gy concurrent radiation at the rate of 1.2 Gy/fraction, 2 fractions/day separated by a gap of 6 hrs, 10 fractions/week, in 6-7 weeks by Theratron -780 E/780C & Bhabhatron-II telecobalt units by bilateral parallel opposed portals. Initial treatment fields included the primary tumor with adequate safe margins and primary nodal drainage region (whole neck). 43.2 Gy was delivered through these fields. Subsequently, field was reduced to spare spinal cord and the primary site was irradiated to a total dose of 72 Gy.

The schedule for hyper fractionation arm was planned by equating the Biological Effective Dose calculations taking conventional value of  $\alpha/\beta=10$  for acute effects and  $\alpha/\beta=3$  for late effects of the radiation.

$BED = D [1 + d / (\alpha/\beta)]$ , where D is the total dose and d is dose per fraction.

3.	<b>51-60</b>	13 (43.33%)	10 (33.34%)	1.302	0.254
4.	<b>61-70</b>	4 (13.33%)	6 (20%)	1.335	0.248
5.	<b>Total</b>	30 (100%)	30 (100%)	-	-

Table II shows that the median age of the patients in the hyperfractionated arm was 52 ( $\pm$  8.30) years with range of 35-63 years while the median age in the conventional arm was 52 ( $\pm$  7.66) years with range of 38-64 years. Total number of patients in each group was 30. The majority of patients were in their 5<sup>th</sup> and 6<sup>th</sup> decades of life.

**Table III Primary site of the tumor**

S. No.	Primary Site	Hyperfractionated Arm	Conventional Arm	$\chi^2$	P value
1.	<b>Base of Tongue</b>	12 (40%)	14 (46.67%)	0.518	0.471
2.	<b>Soft Palate</b>	5 (16.70%)	4 (13.30%)	0.385	0.534
3.	<b>Tonsillo-Lingual Sulcus</b>	3 (10%)	2 (6.70%)	0.652	0.419
4.	<b>Tonsil</b>	5 (16.70%)	7 (23.30%)	1.089	0.296
5.	<b>Vallecula</b>	5 (16.70%)	3 (10%)	1.681	0.194
6.	<b>Total</b>	30 (100%)	30 (100%)	-	-

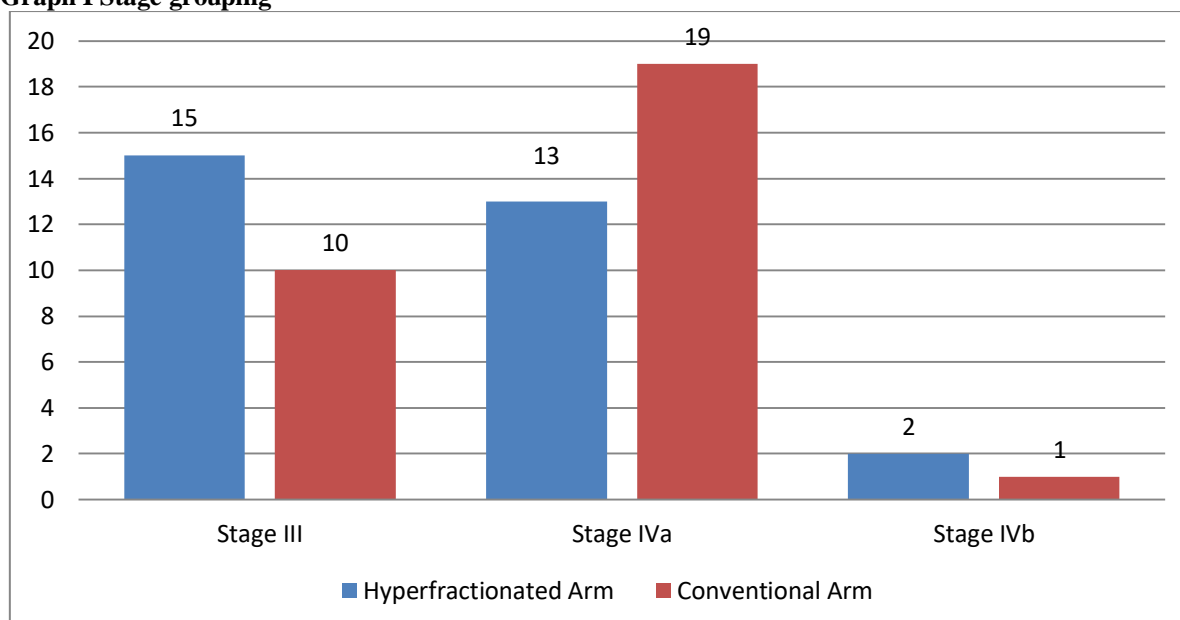
Table III shows that 40% patients in both the arms had the primary of base of tongue. Other common sub-sites were tonsil, soft palate and vallecula.

**Table III Histological Differentiation of the Primary Tumor**

S. No.	Histological Differentiation	Hyperfractionated Arm	Conventional Arm	$\chi^2$	P value
1.	<b>Well</b>	18 (60%)	23 (76.70%)	2.040	0.153
2.	<b>Moderate</b>	11 (36.70%)	7 (23.30%)	2.993	0.083
3.	<b>Poor</b>	1 (3.30%)	0 (0%)	3.330	0.069
4.	<b>Total</b>	30 (100%)	30 (100%)	-	-

Table III shows that well differentiated histology was present in 60% and 76.7% patients in the hyperfractionated and conventional arms, respectively.

**Graph I Stage grouping**



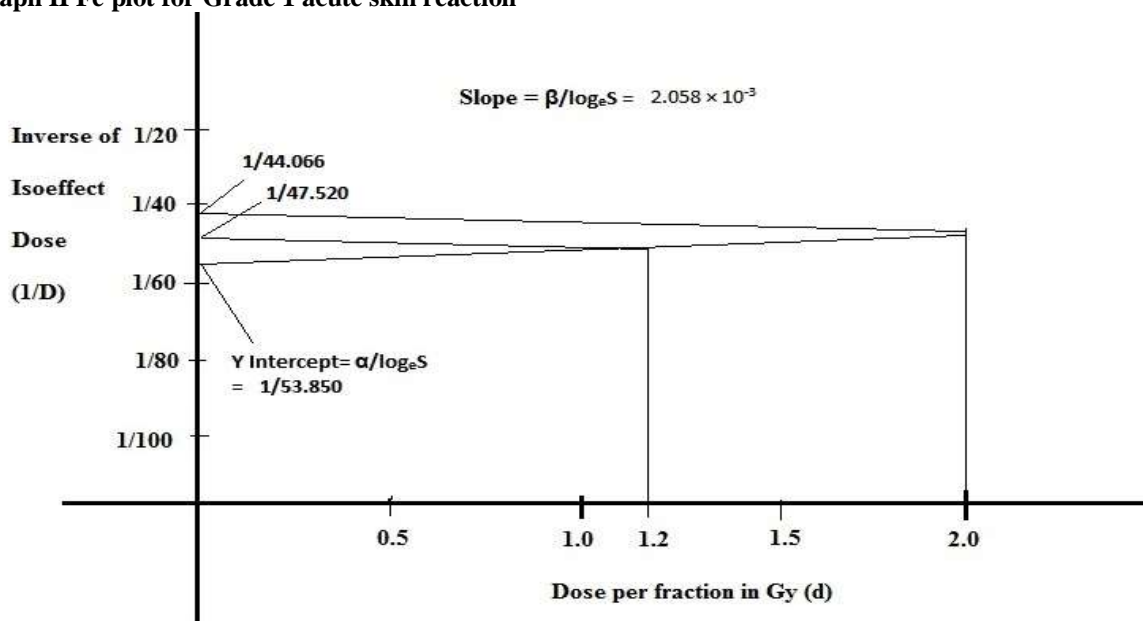
Graph I shows that among the hyperfractionated arm, 50% patients had stage III disease and 43.3% patients had stage IVa disease. In the conventional arm, 33.3% patients had stage III disease and 63.3% patients had stage IVa disease.

**Table IV Mean Isoeffect Dose (Gy) for Acute Skin and Mucosal Reactions**

RTOG GRADE	HYPERFRACTIONATED ARM		CONVENTIONAL ARM	
	Skin	Mucosa	Skin	Mucosa
GRADE 1	47.520	29.840	44.066	27.667
GRADE 2	58.600	46.761	55.000	43.867
GRADE 3	68.000	60.600	62.000	57.466
GRADE 4	-	-	-	-

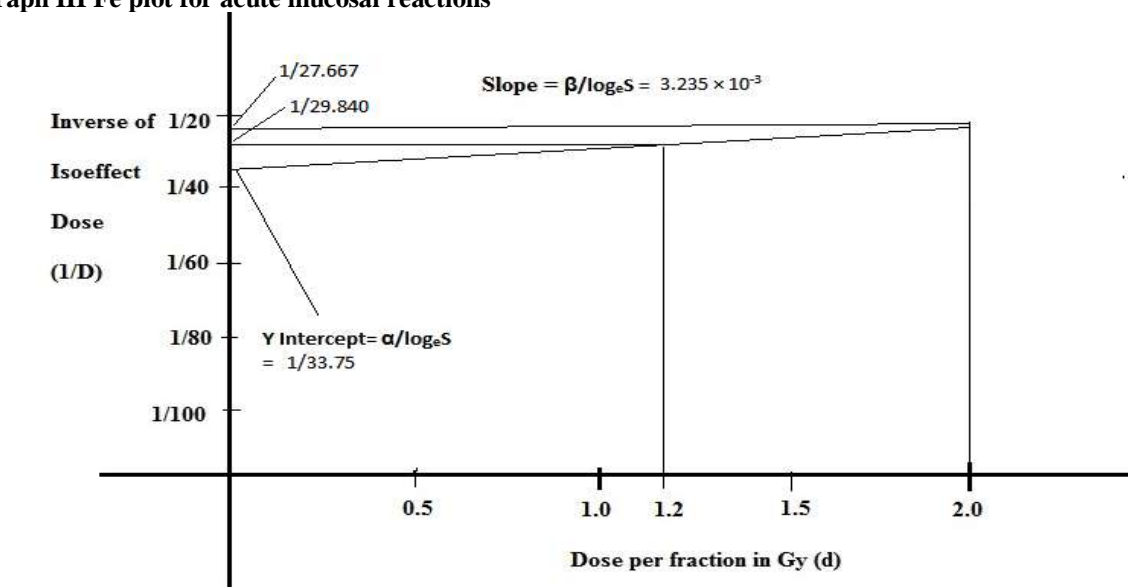
Table IV shows mean Isoeffect Dose (Gy) for acute skin and mucosal reactions.

**Graph II Fe plot for Grade 1 acute skin reaction**



Graph II shows the Fe-plot drawn for the isoeffect doses of grade 1 skin reactions. X-axis depicts the dose per fraction of the treatment schedule and Y-axis shows the inverse of the mean isoeffect dose. The patients of the hyperfractionated arm developed grade 1 skin reaction at the mean isoeffect dose of 47.52Gy, while it was 44.066Gy for the conventional arm. The intercept on the y-axis (1/53.850) obtained by extrapolating the line joining the respective isodose lines corresponds to  $\alpha/\log_e S$  and the slope of the curve ( $2.058 \times 10^{-3}$ ) corresponds to  $\beta/\log_e S$ .

**Graph III Fe plot for acute mucosal reactions**



Graph III shows that the Fe-plot drawn for the isoeffect doses of grade 1 mucosal reactions. X-axis depicts the dose per fraction of the treatment schedule and Y-axis shows the inverse of the mean isoeffect dose. The patients of the hyperfractionated arm developed grade 1 mucosal reaction at the mean isoeffect dose of 29.840Gy, while it was 27.667Gy for the conventional arm. The intercept on the y-axis (1/33.75) obtained by extrapolating the line joining the respective isodose lines corresponds to  $\alpha/\log_e S$  and the slope of the curve ( $3.235 \times 10^{-3}$ ) corresponds to  $\beta/\log_e S$ .

## DISCUSSION

The population of shrinking tumors under the influence of reoxygenation, repopulation, tumor and tissue debris are not expected to behave in a manner similar to cell survival curves from in vitro conditions.<sup>9</sup> Thus, the clinical estimates of regression parameters and time factor for carcinoma of the head and neck would not be expected to be identical to those of  $\alpha/\beta$  of that obtained through cell survival studies.<sup>10</sup> The virtual  $\alpha/\beta$  represent the complex radiobiological phenomena taking place during fractionated radiotherapy incorporating combined influence of cell loss, changing tumor kinetics, clonogen doubling, repair, reoxygenation, blood flow and clearance of the dead and necrotic tissue/ debris and thus could be more appropriate in clinical radiotherapy.<sup>11</sup>

Radiobiological alterations during the course of fractionated radiotherapy are a complex interplay of the "5 Rs" of radiobiology and attempts to represent them in L-Q equation would not only make the L-Q model lose its innocence, but also introduce several parameters with uncertainty in their estimates.<sup>12</sup> This study has tried to represent estimate  $\alpha/\beta$  in oropharyngeal tumors from actual dose-response relations. The estimates derived in this study could be applicable to head and neck cancer treated with teletherapy using 2 Gy per fractions over a 6-7 weeks period with week end gaps. Extrapolating these to head and neck cancer treated with different fractionation schedules may not be appropriate since the dose-response curves could be different for different dose per fractions.<sup>13</sup>

This study was undertaken to estimate the primary tumor regression parameters (virtual  $\alpha/\beta$ ) and linear quadratic model parameter (true  $\alpha/\beta$ ) in patients of head and neck carcinoma undergoing conventional and hyper fractionated external beam radiotherapy using calculated values of BED for acute normal tissue reactions.

Sixty patients of locally advanced, unresectable oropharyngeal carcinoma were randomized to receive concurrent chemoradiotherapy by either conventional fractionation (66 Gy, 2 Gy per fraction, 1 fraction per day, 5 fractions per week, in 6-7 weeks) or hyperfractionated radiotherapy (72 Gy, 1.2 Gy per fraction, 2 fractions per day separated by a gap of 6 hrs, 10 fractions per week, in 6-7 weeks). The patients

of both the arms received concurrent weekly cisplatin ( $40\text{mg/m}^2$ , ceiling dose 50 mg).

Isoeffect doses for the development of RTOG grade specific end point acute skin and mucosal reactions were estimated by regular clinical assessment of the patients during the radiotherapy.<sup>14</sup> Fe-plots were drawn for the isoeffect doses with X-axis depicting the dose per fraction of the treatment schedule and Y-axis depicting the inverse of the mean isoeffect dose. The mean  $\alpha/\beta$  for acute skin and mucosal reactions were 10.005 Gy and 11.086 Gy, respectively. In calculation of  $\alpha/\beta$  by Boer's method, D (mean Isoeffect dose) was plotted on y axis and dD (mean Isoeffect dose X Dose per fraction) was plotted on x axis. The mean  $\alpha/\beta$  for acute skin and mucosal reactions by this method were 10.014 Gy and 11.168 Gy, respectively. In calculation of  $\alpha/\beta$  by Tucker's method, plotting (Dm dm-Dn dn) along x axis and (Dn-Dm) along y axis, where dn=1.2 Gy, dm=2 Gy, Dn represents the isoeffect dose in hyperfractionated arm and Dm represents the isoeffect dose in conventional arm. The mean  $\alpha/\beta$  for acute reactions by this method was 10.228 Gy. Thus, the mean  $\alpha/\beta$  (true  $\alpha/\beta$ ) for acute reactions by all three methods used was 10.454 Gy.

Linear regression method was used to derive the estimates of various coefficients using the model,  $RF = \text{constant} + a_1(D) + a_2(D^2)$ , where RF represents response fraction and D represents total EBRT dose for various cumulative dose intervals. On the basis of this model, the equation  $y = 1.280 - 0.0243x + 0.001x^2$  was derived. The coefficients  $a_1$  and  $a_2$  were assumed to play a role similar to coefficients  $\alpha$  and  $\beta$  of the L-Q dose-effect relationship. The coefficients  $a_1$  and  $a_2$  were therefore not the actual estimates of  $\alpha$  and  $\beta$  respectively, but the ratio  $a_1/a_2$  could be considered to represent  $\alpha/\beta$ . This ratio (virtual  $\alpha/\beta$ ) was calculated to be 3.078 Gy in present study.<sup>15</sup> Further studies involving larger number of patients are warranted to address this topic and to validate the results of present study.

## CONCLUSION

Authors found that the virtual  $\alpha/\beta$  represents the complex radiobiological phenomena taking place during fractionated radiotherapy. It incorporates the combined influence of cell loss, changing tumor kinetics, clonogen doubling, repair, reoxygenation, blood flow and clearance of the dead and necrotic tissue/debris and thus, could be more appropriate in clinical radiotherapy. Any mathematical model used to represent complex biological phenomena should therefore, be based on careful clinical observations to guide treatment.

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