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Original Research

Consequence of Hyper-fractionated Radiotherapy and Concomitant boost Radiotherapy against malignancies located in Head and Neck

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ABSTRACT:
Both concomitant boost radiotherapy and hyper fractionation radiotherapy have been revealed to recover outcomes for patients with head and neck carcinomas. However, both individual approaches moreover increase acute toxicity, and it is doubtful whether anyone can be safely combined.The aim of our study was to find out whether there is any advantage of concomitant boost radiation therapy in controlling head and neck malignancies. The cases were selected from the patients registered at JKCL, LLR and Association hospitals of the G.S.V.M. Medical College, Kanpur. All eligible patients were randomized into two arms as one was conventional group specifying total does of 65 Gy was delivered in $6^1/_2$ week with five fractions per week and 200 cGy per day and another was study group specifying Concomitant boost type hyper fractionation in radiotherapy. Total dose of 65 Gy was delivered in weeks (5 days in a week).Grading of response for measurable lesion were done according to guidelines by WHO. For acute radiation, the toxicity grading, system developed by RTOG &EORTC has been used. The chi square test of significance will be used for Statistical analysis. Malignancies of larynx were successfully controlled by concomitant boost radiotherapy, though the result are not statistically significant because of small number of cases, justifies its use as a better treatment increase in complications. As far as the acute RT reactions are concerned can be controlled using of oral glutamines and amifostine during radiotherapy as Documented**.**
Keywords: Malignancies, Outcomes, Hyper fractionated Radiotherapy, Concomitant Boost Radiotherapy.

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INTRODUCTION

Malignancies of oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, paranasal sinuses, and major and minor salivary glands constitute HNCs, and majority of them arise from the surface epithelium and are squamous cell carcinoma (SCC) (Bose P, et al 2013; Malik, et al. 2017). The dominant risk factors for the development of HNCs are tobacco and alcohol use (Memorial Sloan Kettering Cancer Centre, 2014; Dhull AK et al. 2016; Malik, et al.2017). Addict of Cigarette smoking and alcohol are conventional risk factors for laryngeal cancer (Roni T. Falk et al 1989). Few reviews have recommended that the risk for mutual revelation is larger than that expected from each agent separately (Roni T. Falk et al 1989).

Radiotherapy, chemotherapy and chemo-radiotherapy have been extensively used for the treatment of locally advanced, unresectable head and neck cancer (Loredana Marcu et al 2003). However, objective analysis of an optimal treatment regimen is complicated by the multiplicity of drugs and their interactions with the ionizing radiations (Loredana Marcu et al. 2003). In general, either surgery or radiation is effective as single-modality therapy for patients with early stage disease (Stage I or II) for

most sites (Waes CV, et al 2014, Malik, et al.2017). Radiation may be more effective for controlling the localized primary tumor, because it can be aimed and large doses given, but it is ineffective against disseminated disease. Chemotherapy, on the other hand, may be able to cope with micro‑metastases, whereas it could not control the larger primary tumor (Hall EJ, et al 2012). The rationale for accelerating radiation schedules is predicated on tumor cells undergoing accelerated repopulation during the treatment course after a lag time. Shortening of overall treatment time, lessen the total dose of radiation wasted in compensating for accelerated tumor cell repopulation during treatment (Ahamad A., 2013). Accelerated RT with 6‑fractions a week has shown better response rates than conventional 5‑fractions a week. Locoregional control and overall survival have improved for patients with locoregionally advanced head and neck cancers because of advancements in the delivery of radiotherapy (RT) and concomitant chemotherapy. The aim of our study was to find out whether there is any advantage of concomitant boost radiotherapy radiation therapy in controlling head and neck malignancies. The 2 regimens resulting in improved outcomes are hyper fractionated RT and concomitant boost RT, as demonstrated in the Radiation Therapy Oncology Group (RTOG) (Fu KK, et al 2000; Newlin et al 2010)yet whether altered fractionation can be successfully combined with concomitant chemotherapy to improve the therapeutic ratio without undue increased toxicity remains unknown. Additionally this report scans the effects of smoking and alcohol separately and investigates their interface in a case-control study of laryngeal cancer.

SUBJECT AND METHOD

The cases were selected from the patients registered at JKCL, LLR and Association hospitals of the G.S.V.M. Medical College, Kanpur from February, 2005 to august 2006.The U.I, C.C.T.N.M. staging was used to assess the extent of spread and stage of disease. All eligible patients were randomized into two arms. ARM I is conventional group specifying total does of 65 Gy was delivered in $6^1/_2$ week with five fractions per week and 200 cGy per day. Spinal cord was excluded from the field after a total dose of 4500 cGy in $4^1/_2$ weeks and rest of the dose was delivered with reduced field excluding neck node if not involved clinically. ARM II is study group specifying Concomitant boost type hyper fractionation radiotherapy. Total dose of 65 Gy was delivered in weeks (5 days in a week). For Initial 3 weeks: 200 cGy per fraction 5days a week to a basic large field (between 8-8.30 am). For remaining 2 weeks: 200 cGy per-fraction 5day a week to basic large field(between 8-8.30 am) followed by a boost of 150 cGy per-fraction 5day a week to a small field encompassing the primary lesion only, will be delivered 5-6 hours after the treatment of basic large field (between1.30-20 pm).

CRITERIA FOR SELECTION OF PATIENTS

The Patients with tumors of larynx of any stage were included in the study; Nodal status may be any (N0-N3); Patients did not have any metastasis at initiation of treatment i.e. were Mo.; Patients had not have undergone any surgical treatment and chemotherapy previously; There was no medical contraindication to radiotherapy; Two arms were balanced with respect to age, sex, T-stage Karnofsky performance (>70), pre-treatment Hb level was >10gm.

PRE-EVALUATION

General evaluation includes detailed history, physical examination and laryngoscopy (direct and indirect). Hematological evaluation includes Hemogram (HB, TLC, DLC, platelet count, BT & CT; LFT (liver function test); RFT(renal function test). Radiological evaluation includes Chest X-ray (PA view); X-ray neck lateral view for soft tissue and bony/cartilage involvement. The CT scan (plain and contrast) and MRI done for selected cases. Direct laryngoscope guided biopsy was done followed by histopathological examination and subsequent grading, FNAC from any cervical lymph node. Node measuring >15 cm considered positive for metastasis.US guided FNAC in case of doubtful neck nodes. During treatment patient was observed weekly for skin reaction, tumour response, laryngeal edema, and taste sensation, loss of hair and any other symptom or sign.

GRADING

Grading of response for measurable lesion were done according to guidelines by WHO, 1982.For acute radiation, the toxicity grading, system developed by RTOG &EORTC has been used (valid from day 1 to day 90); for late reactions grading were done (after 90 days) according to RTOG grading.

STATISTICAL ANALYSIS

The chi square test of significance will be used to determine whether the observed results are statistically significant or not. P value less than 0.05 is significant P value less than 0.01 is highly significant.

RESULT

According to various age groups Maximum numbers of cases were between 41-70 yrs. Age group in both the groups. In conventional group one case is below age of 30, one belong to age group between ages of 31-40,six from 41-50, two from 51-60 and ten from the age group of 61-70 however cases from age group 70 and above is nil. In study group same no of cases were observed from age group unto 40, however the case between age of 41-50 was three, eight from 51-60, five from 61-70 and two from 71 and above age. The male cases are dominant over female in both arms with ratio of 19:1.

Table 1: Distribution of cases according to TNM staging

Stage	No. of cases	TNM Stage	Conventional Group	Total	Study group	Total
I	7	$T_1 N_0M_0$	5	5	2	2
II	7	$T_2 N_0M_0$	3	3	4	4
III	13	$T_3 N_0M_0$ $T_1 N_1M_0$ $T_2 N_1M_0$ $T_3 N_1M_0$	- 1 1 2	4	7 - - 2	9
IV	13	IVA- $T_4 N_0M_0$ $T_4 N_1M_0$ Any TN_2M_0	2 - 4	6	1 - 3	4
		IVB Any $TN_3 M_0$	2	2	1	1
		IVC Any T Any N M1	-	-	-	-
Total	**40**			**20**		**20**

Table 2: Comparison of the tumor response between conventional group and study group according to TNM stages

Stage	Conventional group					Study group				
	n	CR	PR	NR	DR	n	CR	PR	NR	DP
I	5	3 (60%)	1 (20%)	3 (60%)	-	2	3 (60%)	-	-	-
II	4	3 (75%)	1 (25%)	-	-	4	3 (60%)	-	3 (60%)	-
III	3	2 (67%)	1 (33%)	-	-	9	3 (60%)	3 (60%)	-	-
IV	8	2 (25%)	3 (37.5%)	2 (25%)	1 (12.5%)	5	3 (60%)	3 (60%)	3 (60%)	1 20%
Total	**20**	**10 (50%)**	**6 (30%)**	**3 (15%)**	**1 (15%)**	**20**	**14 (70%)**	**3 (15%)**	**2 (10%)**	**1 (5%)**

Table 3: Tumor response according to histopathologically and grade

Histo-Pathology Grade	Conventional group					Study group				
	No .of cases	CR	PR	NR	DP	No. of cases	CR	PR	NR	DP
Sq. cell Ca.gl-I	7	4	2	1	-	4	2	-	-	1
Sq. cell Ca.gl-II	9	4	3	2	-	10	8	1	1	-
Sq. cell Ca.gl-III	-	-	-	-	-	3	1	2	-	-
Sq. cell Ca.gl-IV	3	2	-	-	1	2	1	-	1	-
Deno sq. ca	1	-	1	-	-	1	1	-	-	-
Total	**20**	**10**	**6**	**3**	**1**	**20**	**14**	**3**	**2**	**1**

Table 4: Comparison between incidence of acute RT reactions in conventional group and study group

		Grade I	Grade II	Grade III	Grade IV
Skin Reactions	Conventional Group	10-70%	0-40%	0-20%	Nil
	Study Group	0-60%	0-30%	0-40%	0-10%
Salivary Gland Reactions	Conventional Group	30-70%	20-40%	0-10%	Nil
	Study Group	0-40%	0-25%	10-50%	0-10%
Laryngeal Reactions	Conventional Group	20-60%	20-30%	0-20%	Nil
	Study Group	10-30%	0-25%	0-50%	Nil

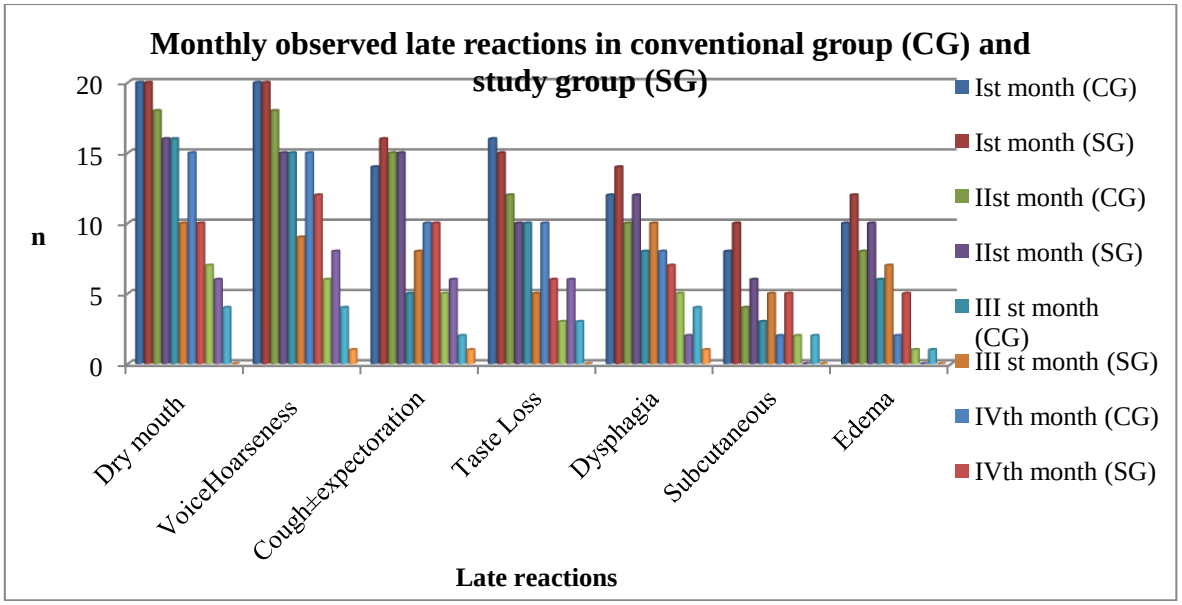

Figure 1: Monthly observed late reactions in conventional group and study group

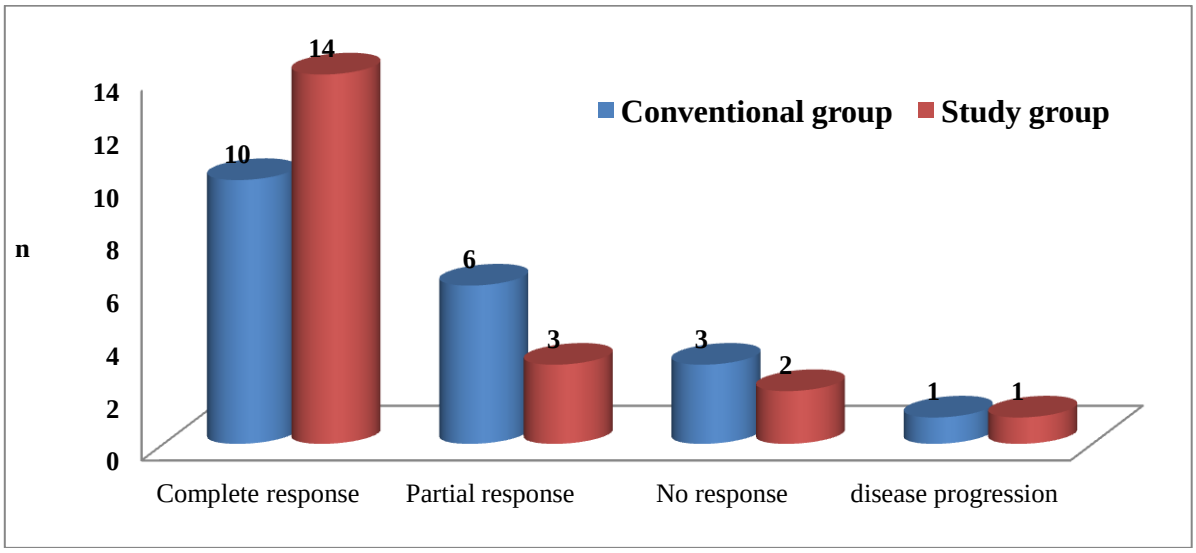

Figure 2: Distribution of results between conventional group and study group

DISCUSSION

The majority of patients gave history of addition (i.e. smoking, chewing and both) (95%). Maximum number of carcinoma larynx cases was addicted for Bidi/cigarette smoking (65%). The maximum numbers of cases were of squamous cell carcinoma grade II (47.5%). Two cases were of adeno-squamous carcinoma (5%) in each grade. It is evident from the data of Table 1 that most of the cases were TNM stage III and IV. Table 2 summarises the comparison of the tumor response between conventional group and study group according to TNM stages. From the Table 2, in stage I, complete response is 60% in conventional group while 100% in study group. In stage II, complete response is 75% in both groups. In stage III, complete response is 67% in conventional group while 78% in study group. In stage IV, complete response is 25% in conventional group while 40% in study group. Over all result showed complete response in 50% case in conventional group while 70% complete response in study group. The 'p' value is more than 0.05%, which is insignificant and this may be due To number of reasons of reasons and one may be the less number of cases in our study. From Table 3, in stage I, complete response seen in 59% cases is conventional group while in 75% cases in study group. In stage II, complete response seen in 44% cases is conventional group while in 80% cases in study group. In stage III, complete response seen in 33% cases. In stage IV, complete response seen in 66% cases is conventional group while in 50% cases in study group. Overall complete response was 50% conventional group while 70% in study group(Jeremic B, et al 1997; Jeremic B, et al 2000; Garden AS, et al 2008; Ang KK, et al 2003).

From Table 4, Grade III skin reaction observed in IVth week. Which get subside Later on. Maximum number of patients with grade I reactions was during IVth

week while Grade III reaction was observed during IV^{th} and V^{th} weeks of RT. Maximum number of patients with Grade I-Grade III reactions was during IV^{th} week of RT. Grade IV laryngeal reaction was not observed during whole course of RT. Maximum numbers of patients within Grade I- Grade IV reactions were during IV^{th} andV^{th} week of RT. Grade IV skin reaction was not observed during IV^{th} andV^{th} week of RT. Grade IV salivary gland reactions were observed in 10% cases during IV^{th} and V^{th} week of RT. Grade IV laryngeal reactions were observed mostly in IV^{th} and V^{th} week of RT (Figure 1and Figure 2). No patient had grade IV RT reactions. There is increase in Grade III and Grade IV RT reactions in study group (Schoenfeld GO, et al 2008; Jeremic B, et al 2000; Ang KK, et al 2003; Machtay M, et al 2008). On monthly observed late reactions in conventional group20 patients came for follow-up and only 8 patients' up to 6 months (Figure 1). On monthly observed late reactions in study group 20 patients came for follow-up and only 6 patients' unto 6 months (Figure 1).

CONCLUSION

The aim of our study was to find out whether there is any advantage of concomitant boost radiotherapy radiation therapy in controlling head and neck malignancies and if there is no advantage then too whether it is equally effective because in that case also there will be benefit of saving treatment duration by $1^1/_2$ week which is an important achievement. After completing the study following conclusions have been drawn. Here the Carcinoma larynx comprised of14.84% (129) of total head and neck cancer cases (869) and 3.8% of total cancer cases (3392). The predominantly affected age group was between 41-70 yrs which is younger as comparison to that reported in western literature. Males of are more commonly affected than females. Most of the patients had addiction habits of bidi /cigarette smoking with increased frequency and duration. About 65% of the cases belonged to advanced stages of disease (stage III & IV).Most common histopathology was grade II squamous cell carcinoma. There was a definitive advantage in controlling carcinoma larynx cases by concomitant boost radiotherapy. The results were 70% CR with concomitant boost and 50% CR with conventional fractionation. Although 'p' value is insignificant which may be due to many reasons and one of them in our study may be small sample size. There was a clear cut advantage of concomitant boost RT in advanced stage carcinoma larynx cases. Acute RT reactions as expected were more frequently observed in concomitant boost RT group (study group) as compared to those in conventional fractionation group (conventional group), but none of them were severe enough to cause difficulty in completing the treatment. There was no significant difference in late reaction as observed in our study. To summarize, malignancies of larynx were successfully controlled by concomitant boost radiotherapy, though the result are not statistically significant because of small number of cases, justifies its use as a better treatment increase in complications. As far as the acute RT reactions are concerned can be controlled by use of oral glutamines and amifostine during radiotherapy was supported by Dr. T.G.Wendtand Dr. E.Y.Huang individually.

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STATEMENT OF CONFLICT OF INTEREST

In the opinion of the author, there was no conflict of interests.

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