

Comparison of Locoregional Control, Acute Radiation Toxicities and Patient Compliance between Two Different Radiation Fractionation Schedules with Concurrent Chemotherapy in Oropharyngeal Cancer

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ABSTRACT

Introduction: Irrespectively of the modality of primary treatment for head and neck squamous cell carcinoma, local or locoregional residual or recurrent tumors represent the major cause of treatment failure, emphasizing the role of locoregional control for the patients' long-term survival. The study compares HFRT-CT and CTRT in stage III and IV carcinoma of oropharynx.

Material and Methods: Study arm (HFRT-CT) 1.1 Gy per fraction, two fractions daily with a minimum interfraction interval of 6 hours, five days a week up to a total dose of 72.6 Gy in 66 fractions over 6-6 1/2 weeks and in the control arm (CTRT) 2 Gy per fraction, single fraction a day, five days a week to a total of 66Gy, over 6-6 1/2 weeks, both the arms use concurrent chemotherapy with injection cisplatin 40mg/m² weekly.

Results: At the end of 6th week 28 patients in the HFRT-CT arm and 29 patients in CTRT arm were available for evaluation. In the HFRT-CT arm 24/28(85.7%)patients and in the CTRT arm 21/29(72.4%)patients showed complete response for primary. For nodal disease a complete response of 92.85% and 89.65% were seen in HFRT-CT and CTRT arm respectively. At the 6th week out of the 16 stage III patients in the HFRT-CT arm 13 had complete response(81.3%) and 3 patients had a partial response (18.7%) and out of the 12 stage IV patients 9 patients had a complete response and 3 patients had partial response.

Conclusion: Hyperfractionated radiotherapy with concurrent chemotherapy in locally advanced carcinoma, can be delivered with manageable toxicities. A trend towards better outcome for patients having T4 or N3 disease is noted, even though a statistical significance could not be seen.

Keywords: Accelerated Radiotherapy, Head and Neck Carcinoma, Radiation Therapy, Radiotherapy Fractionation Schedules

neck cancers is more in males, some studies in head and neck cancer radiotherapy show that, females have a better response rate. In RTOG -90-03 study this trend is reflected in the conventional arm.⁵ Head and neck carcinomas include tumors of oral cavity, pharynx and larynx.⁶ At least 95% of Head and Neck carcinomas are squamous cell carcinoma.⁷ The different treatment modalities available are Radiation, Surgery, Chemotherapy and Monoclonal antibodies. The treatment of patient is individualized. In advanced stages the treatment is multimodality. Patients with advanced disease usually present with locoregional recurrence or persistent disease.⁸ In many patients with locally advanced operable disease surgery and postoperative radiation offers optimal locoregional control.⁹ Head and neck surgery has advanced greatly to the extent that voice restoration and voice preservation are now possible after larynx and pharynx surgeries. The prognosis of advanced oropharyngeal cancers is poor. Survival rates at 5 year with conventional radiation therapy and or surgery is around 30%, at best, for lesions of stage III and stage IV.¹⁰ Horiot et al reported the results of EORTC Trial 22791; conventional fractionation was compared with hyperfractionation (80.56Gy in 1.15 Gy bid) in T2—T3 N0 -N1 (<3cm) oropharyngeal cancers, base of tongue lesions were excluded.¹¹ A significant improvement in 5 year locoregional control was observed, which did not translate into a corresponding survival gain. Several methods were tried to improve this result. These are high LET, hyperbaric oxygen, hypoxic cell sensitizers and altered fractionation schedules. Altered fractionation schedules with strong radiobiological basis are accelerated hyperfractionation and hyperfractionation.¹² Hyperfractionation involves use of smaller doses per fraction given 2 or 3 times daily in approximately same overall time as with conventional radiation. Main goal of

INTRODUCTION

In India, Head and Neck carcinomas account for 30-50% of all malignancies.¹ Squamous cell cancer of the head and neck accounts for approximately 5% of newly diagnosed cancer, that is, 6,44,000 cases and over 3,50,000 cancer deaths, worldwide each year.² Approximately 40% to 60% of patients develop local recurrences and 20% to 30% will be diagnosed with distant metastatic disease.³ It is seen more in males, owing to tobacco smoking and chewing. Tobacco contains 3000 different chemicals out of which 40 are putative carcinogens.⁴ These carcinogens include polynuclear aromatic hydrocarbons, n-nitrosamines, organic (Eg. benzene) and inorganic (Eg arsenic) compounds and polonium 2104. Even though the incidence of head and

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hyperfractionation is to increase therapeutic differential between late responding normal tissues and tumor, which allows for increase in the total dose with better local control without risk of late tissue complications.¹²

The study compared hyperfractionated radiation with concurrent chemotherapy and conventional fractionated radiation with concurrent chemotherapy in stage III and IV carcinoma of oropharynx.

MATERIALS AND METHODS

This was a prospective clinical trial which compared hyper fractionated radiation with concurrent chemotherapy with conventional fractionated radiation with concurrent chemotherapy in stage III and stage IV oropharyngeal squamous cell carcinomas. Study group and control group consisted of patients registered in the Department of Radiotherapy, Medical College Trivandrum. The study group and control group were matched for age, sex, performance status and tumor status. Group I (HFRT-CT) consists of patients with locally or regionally advanced Ca Oropharynx treated with weekly Inj Cisplatin along with hyper fractionation. Group II (CTRT) consists of patients with locally or regionally advanced Ca Oropharynx treated with conventional fractionated radiation with weekly Inj cisplatin, Inclusion criteria: Patients with biopsy proven stage III and stage IV squamous carcinoma of the oropharynx, patients with age less than or equal to 70years, patients without previous history of cancer or treatment for cancer, pretreatment ECOG performance status less than 3. Exclusion criteria: Presence of distant metastasis, age more than 70 years, performance status more than or equal to 3, history of cancer or treatment for cancer. Patients were evaluated by physical examination, ENT examination, necessary laboratory and radiological evaluation. Routine blood counts, liver function test, renal function test, chest X-ray, indirect and direct laryngoscopy were carried out to determine the extent of the tumor and staging. Biopsy of the tumor was done in all cases for confirmation and FNAC of the lymph nodes were done when indicated. CT scan and MRI scan were considered optional. The clinical staging was confirmed by the Principle investigator. All the patients were informed about the treatment protocol and written consent was obtained from all patients. In the study arm 1.1 Gy per fraction, two fractions daily with a minimum interfraction interval of 6hours, five days a week upto a total dose of 72.6 Gy in 66 fractions over 6-6 1/2 weeks and in the control arm 2 Gy per fraction, single fraction a day, five days a week to a total of 66Gy, over 6-6 ½ weeks, both the arms use concurrent chemotherapy with injection cisplatin 40mg/m² weekly. Both groups used injection cisplatin 40mg/m² weekly, that is, given on Mondays as the concurrent chemotherapy agent. The study compares these two arms with locoregional control, acute radiation toxicities, and patient compliance. Patients were evaluated for response to treatment, both primary and lymph nodes at 3 weeks and 6 weeks of completion of treatment.

RESULTS

A total of 32 patients enrolled in the HFRT-CT arm, 33 patients enrolled in CTRT arm. The two group of patients were comparable with respect to all pre-treatment characteristics which were confirmed by statistical analysis.

The age distribution was comparable in both the groups.(P value 0.655). In the study group there were 28 males and 4 females and in the control group there were 28 males and 5 females. Patients in the two groups had performance status of 1 and 2. The symptoms of the patients that were recorded in both the groups were pain, dysphagia, sore throat, neck mass, hoarseness of voice, difficulty in protrusion of tongue, ear pain, trismus, fever and cough. In both the HFRT-CT group and the CTRT arms the majority of the cases belonged to the base of the tongue. The next common site was the tonsil. In the HFRT-CT arm, a male patient who had stage III base of tongue cancer, with complete response at third week presented with a proliferative growth of size 1x0.5 cm at the tip of the tongue during the 6th week of follow up and was subsequently biopsy proved as squamous cell carcinoma. He was a smoker as well as a tobacco chewer. The distribution of the control arm and the study arm were comparable with a p value of 0.82.Majority of the cases were exophytic growths with ulcerative component and pure infiltrative lesions were rare. Histologically the lesions were divided into well differentiated, moderately differentiated and poorly differentiated. Histology was studied from the biopsy of the primary lesion and FNAC was done in lymph nodes whenever necessary. The distribution was comparable and the p value was 0.827.The pretreatment hemoglobin was recorded in two groups, that is, into >12 mg% and 10-12 mg%. The majority of patients in the HFRT-CT group had Hb 10-12 mg %and in the CTRT arm had Hb 10-12 mg%. Both the groups were comparable in this distribution, with a p value of 1.In the study group the distribution according to the tumor status is as follows, 15.6% of patients had T1 tumor, 50% had T2 tumor, 28.1% had T3 tumor and 6.3%had T4 tumor. In the control arm 18.2% had T1 tumor, 39.4%had T2 tumor, 36.4% had T3 tumor and 6.1% had T4 tumor. Majority of patients in both group had T2tumor. The distribution was comparable and had a p value of 0.901. The distribution of the nodal status was as follows-in the study arm6.3% of patients had N0 node, 50%had N1 node, 34.4%had N2 node and 9.4% had N3 node. In the control arm, 18.2% had N0 node, 51.5% had N1 nodes, 24.2% had N2 nodes and 6.1% had N3 nodes. The distribution was comparable in both the arms, with a p value of 0.476.In the HFRT-CT arm there were 16 patients with stage III disease and 16 patients in stage IV disease, and in the CTRT arm there were 21 patients with stage III and 12 patients with stage IV disease. All the patients in both group developed grade I and grade II mucositis. In the HFRT-CT group 62.5% patients developed grade III mucositis and in the CTRT arm 30.3% patients developed grade III mucositis. In the HFRT-CT arm more grade III mucositis was observed in stage IV (60%) as compared to stage III (40%); 12 patients out of the 20 patients who developed grade III mucositis belonged to stage IV. This trend was not observed in the CTRT arm. All patients in the two groups developed grade I skin reactions, 31.3% of patients in the HFRT-CT arm and 33.3% of patients in the CTRT arm developed grade II skin reaction. No patient in either arm developed grade III or grade IV skin reaction. All the patients in the HFRT-CT group developed pain in the throat during the treatment. These patients also had discomfort and difficulty in swallowing. Out of the 32 patients in the HFRT-CT arm, 21 patients had hoarseness of voice. In the CTRT group out of the 33 patients 31 had

discomfort and difficulty in swallowing. Dry mouth was experienced in all patients in the HFRT-CT arm and the CTRT arm. A greater percentage of patients in the HFRT-CT arm had control of pain only with narcotics when compared to the CTRT arm. In the HFRT-CT group 71.9% of patients had treatment break. In the CTRT arm, only 39.4% patients had interruption of their radiation treatment. The most common cause of treatment break was mucositis. The break duration extended from 7 to 14 days. The other causes of treatment break are count drops, fever, personal reasons etc. The patients who had grade III mucosal reactions were given 1 week break. During this break period patient was admitted in our ward and given hydration and other supportive treatment. The treatment breaks were divided into break in radiation treatment and chemotherapy. The patients were not given chemotherapy during radiation break week. There was more radiation interruption in the hyper fractionated arm compared to the conventionally fractionated arm, the most common reason being mucositis. This was statistically compared and a p value of 0.013 obtained. The break duration was divided into a break of less than or equal to 1 week or more than 1 week. These differences in the distribution of break, were analyzed statistically and a p value of 0.029 obtained. The reason for radiation break was analyzed in both arms and the most common reason was mucositis. The other reasons for the break were low blood count, fever or other personal reasons. We gave a break of one week, for all patients with mucositis grade 3. When radiation is withheld for 1 week due to mucositis, chemotherapy was also withheld. The other reasons for not taking chemotherapy were drop in the blood count and absence of the patient due to some personal reasons. The difference in the break in the two arms were studied statistically and a p value of 0.033. The most common reason of chemotherapy break was radiation break which was mostly due to grade III mucositis. Out of the 23 patients in the HFRT-CT arm, with chemotherapy break, associated with radiation break 10 patients had other reasons like count drop or other personal problems. In the CTRT arm, out of 13 patients with chemotherapy break associated with radiation break, 3 patients had other reasons also.

Control of the primary at 3rd week in both the arms all patients with T1 and T2 tumors had complete response. In the hyperfractionated radiation arm out of the 9 patients with T3 disease 6 patients had complete response and 3 patients had partial response. In the conventional radiation arm out of the 12 patients 6 patients had a complete response and 6 patients had partial response. In the hyperfractionated radiation arm out of the 2 patients with T4 disease 1 patient had a complete response and 1 patient had a partial response. In the conventional radiation arm 2 patients had T4 disease and both patients had a partial response. So a total of 28 /32 (87.5%) patients in the HFRT-CT arm had a CR and 25/33 (75.8%) in the CTRT arm. The difference in the response rate was statistically studied and the p value is not significant, 0.33. Control of the Primary at 6th week, 28 patients in the study arm and 29 patients in the control arm were available for evaluation. Out of the 8 patients with T3 disease in the study arm, 5 patients had complete response and 3 patients had a partial response. In the control arm out of the 12 patients with T3 disease 6 patients had a complete response and 6 patients had a partial response. All the patients with T4 disease were available for evaluation and all of them maintained the same

response status. In the HFRT-CT arm 24/28 (85.7%) and in the CTRT arm 21/29(72.4%) patients showed complete response. The p value is 0.33, which is not significant.

Control of the Node at 3rd week in the study arm all 16 patients with N1 disease showed complete response. In the control arm out of the 17 N1 patients 16 patients had a complete response and 1 patient had a partial response. Out of the 11 patients with N2 disease in the study arm 10 patients had a complete response and 1 patient had a partial response. On the control arm out of the 8 patients with N2 disease 6 patients had a complete response and 2 patients had a partial response. Out of the 3 patients with N3 disease in the study arm 2 patient had a complete response and 1 patients had a partial response. In the control arm 2 patients had N3 disease and 1 patient had a complete response and 1 patient had a partial response. In the HFRT-CT arm 30/32 (93.7%) and in the CTRT arm 28/33 (84.8%) patients had a complete response. This difference was not statistically significant.

Control of Node at 6th week, 28 patients in the HFRT-CT arm and 29 patients in the CTRT arm were available for evaluation. In the HFRT-CT arm out of the 16 patients with N1 node, all patients had complete response. In the CTRT arm out of the 14 patients with N1 node, 13 had complete response and 1 patient had partial response. In the HFRT-CT arm there were 7 patients with N2 node, 6 patients had complete response and 1 patient had partial response. In the CTRT arm there were 7 patients with N2 node, 6 had a complete response and 1 had a partial response. In the HFRT-CT arm out of the three N3 nodes, 2 showed a complete response and 1 showed a partial response. In the CTRT arm out of the two N3 nodes present, 1 had a complete response and 1 had a partial response. In the HFRT-CT arm, 26/28 patients and in the CTRT arm, 26/29 patients showed complete response in the 6th week and there was no statistical significance between the two arms.

Control of the disease stage-wise at 3rd week in the HFRT-CT arm, stage III patients were a total of 16 patients, out of which, 13 patients showed a complete response and 3 patients a partial response. In stage IV patients out of 16 patients in the study arm, 13 showed a complete response and 3 showed a partial response. In the CTRT arm out of 21 stage III patients, 15 patients had a complete response and 6 patients had a partial response. Out of the 12 stage IV patients in the control arm, 7 patients had a complete response and 5 patients had a partial response. In the HFRT-CT arm, stage III and stage IV are showing a trend towards increased response when compared to the CTRT arm. This distribution was statistically analyzed and the p value for stage III between the arms is 0.76 and for stage IV is 0.36, both values not significant. In the HFRT arm 26/32 (81.3%) and 22/33(66.6%) obtained a complete response, when both the stages are taken together.

Control of the disease stage wise at 6th week, 28 patients were available for evaluation in the HFRT-CT arm and 29 patients in the CTRT arm. In the HFRT-CT arm out of the 16 stage III patients, 13 patients had a complete response and 3 patients had a partial response and out of the 12 stage IV patients, 9 patients had a complete response and 3 patients had a partial response. In the CTRT arm out of the 18 stage III patients, 12 patients had a complete response and 6 patients had a partial response and out of the 11 patients having stage IV disease, 7 patients had complete response and 4 patients

had a partial response. The p values for both the stages were analysed with respect to response in the two arms and p values of 0.82 and 0.89 were obtained for stages III and IV respectively, which are not statistically significant. The relationship of age group and gender with complete response was studied statistically and the p values for the HFRT-CT arm and CTRT arm are not statistically significant. In both the study arm and the control arm there were both radiation treatment breaks and chemotherapy breaks. The most common cause of radiation break as well as chemotherapy breaks was mucositis. A break of one week was given for all patients with grade III mucositis, while they were admitted in the ward and given supportive treatment. No patient in either arm developed grade IV mucositis. The impact of the treatment breaks in the outcome is analyzed. The influence of radiation break duration with respect to the response of node was studied statistically and a significant p value of 0.014 obtained, which shows that response rate decreases with an increase in the duration of break. The influence of radiation break with respect to the duration of break analyzed statistically and significant p values of 0.015 and 0.031 were obtained for HFRT-CT and CTRT arms respectively. The difference in the response of T3 and T4 tumor as a function of Chemotherapy break was analyzed and a p value of 0.355 was obtained which was not significant. The influence of Chemotherapy break duration with respect to the response of node was studied statistically and an insignificant p value of 0.87 was obtained. The break in the chemotherapy did not significantly affect the control of composite disease, with a p value of 0.13 in the HFRT-CT arm and 0.23 in the CTRT arm.

DISCUSSION

The overall response rate in the studies with hyperfractionated radiation and chemotherapy ranged from 63.5%¹³ to 92.5%¹⁴ with better response for T3 lesions and modest response for T4 lesions. Glanzmann et al showed a complete response of 66.7% for T3 tumors and 65.5% for T4 tumors.⁸² In our study we have used hyper fractionation with 110c Gy per fraction, two fractions a day with an interfraction interval of minimum 6 hours, 10 fractions a week. This schedule has been tried by many researchers in altered fractionation. James Fontanesi has used 110cGy, two times a day up to a total of 60-76.35Gy in stage III and stage IV of head and neck squamous cell carcinomas with concurrent cisplatin.¹⁵ Jampolis et al in advanced lesions of the head and neck has used 120 cGy B/D up to a total of 70 Gy.¹⁶ Parson et al observed severe mucositis in 20% of patients which markedly interfered with the ability to maintain adequate nutrition, with 15 patients having to put ryles tube.¹⁷ According to Parson et al tolerance to hyperfractionated radiation improved with limiting the volume that receives the full dose by shrinking the fields, differential weight age and wedges.¹⁷ In our study the shrinking field technique is used, by shrinking the field to protect the spinal cord at 42 Gy in 21 fractions in the control arm and 41.80 Gy at 38 fractions. Pinto et al observed a complete response of 82% in patients with oropharyngeal cancer, by giving a total dose of 7040 cGy.¹⁸ With concurrent chemotherapy and radiation, in a study by Marcial et al¹⁹ observed a complete response 68% of patients with T3 disease. Jampoli S et al²⁰ has observed higher complete response for T4 disease. With

follow up Rodney et al¹² reported local control of 38% for T4 lesions treated with hyperfractionation. Jampoli S et al²⁰ has observed higher complete response for T4 disease (72%) in the hyperfractionated arm. The overall response rate in the studies with hyperfractionated radiation and chemotherapy ranged from 63.5%¹³ - to 92.5%¹⁴ with better response for T3 lesions and modest response for T4 lesions. In our study in the HFRT-CT arm there were 9 cases with T3 disease and 2 patients with T4 disease and the CR of T3 and T4 disease at 3rd week are respectively 66.7% and 50%, and the CR at 6th week are 62.5% and 50% respectively. The CR of T3 at 3rd and 6th weeks in the CTRT arm are 50% and 50%. A conclusion regarding the superiority of the HFRT-CT radiation cannot be made from this study because of the less number of patients evaluated in this study and also due to the short follow up of this study. It was found that radiation break was found to affect the significantly the response of both HFRT-CT and CTRT arms, with p values of 0.015 and 0.031 respectively. Cox et al analyzed treatment breaks on the control of the local control and found that a treatment break of more than 10 days affected the control significantly due to accelerated repopulation.²¹

CONCLUSION

The disease control with hyperfractionated radiation with weekly chemotherapy shows better results when compared to conventional radiation with weekly chemotherapy in our population. For moderately advanced operable disease, hyperfractionated radiation has resulted in the preservation of the organ and its function and helped in improving the quality of life. Improved control was better appreciated in T4 disease and N3 nodes even though the number of patients with this advanced disease was few and no statistical significance obtained. Though the patients had more acute reactions in the hyperfractionated arm, these could be tolerated with symptomatic and supportive treatment. In this study we have observed that the treatment compliance and tolerability is improved, by introducing ryles tube from the beginning of hyperfractionation and by removing it only after 10 days of completion of treatment. The patients in both groups had control of their acute toxicities at the 6th week except for some patients with hoarseness of voice. A negative influence of radiation break and its duration to the tumor response was seen and confirmed statistically; no such influence was seen with chemotherapy break. Dose escalation with CT planning and shrinking field technique with hyperfractionation and concurrent chemotherapy would further improve the local control in locally advanced disease. The objective response assessment, by histopathological examination of primary site at the end of treatment and meticulous attention to prevent treatment breaks may bring out better and more reliable results. The long term toxicities of the treatment are not studied and long term follow up is needed to know the survival benefits and late tissue complications.

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