Comparison of Conventional Radiotherapy with Accelerated Fractionation Radiotherapy in Squamous Cell Head and Neck Cancers – A Prospective Study

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ABSTRACT

Introduction: Head and neck carcinoma is the most common cancer. Radiotherapy along with concurrent chemotherapy has long been the standard nonsurgical therapy for locally advanced disease. State of the art regarding radiation dose fractionation has evolved from once daily treatment to hyper fractionation and accelerated fractionation. The aim of the study was to assess the treatment response by locoregional control and radiation toxicity resulting from conventional and accelerated fractionation radiotherapy in squamous cell head and neck cancers.

Material and methods: In both arms,25 patients were recruited for the study .Six fractions per week of radiation were given in Accelerated fractionation (arm A) and five fractions in the conventional group (arm B).All patients received a radiation dose of 66 Gy /200 cgy/#/in 33 fractions. No chemotherapy was administered

Results: During and immediately after the end of radiation treatment, the patients were assessed for locoregional control and radiation toxicity .78% of the patients in accelerated fractionation arm and 72% of the patients in conventional arm showed complete response .Radiation toxicities were slightly higher in accelerated fractionation compared to conventional fractionation radiotherapy

Conclusion: Improved locoregional control was observed in the accelerated arm .The radiation toxicities were higher in the accelerated arm but they were acceptable and controllable. Overall accelerated fractionation is a better choice of radiation treatment in squamous cell head and neck cancers.

Keywords: Head and Neck Cancer, Conventional Fractionation, Accelerated Fractionation, Radiation Toxicity.

INTRODUCTION

Head and neck carcinoma is the sixth most common cancer accounting for 20% -30% of all cancers. Of these, Carcinoma of Oropharynx leads the list.[1] Concurrent Chemo Radiation (CCRT) is the standard of treatment in locally advanced head and neck cancer.[2] However chemotherapy is not without its hazards with safety concerns precluding its administration in elderly patients, those with preexisting medical problems (with abnormal or subnormal renal,hepatic or bone marrow function) and in patients who refuse chemotherapy.[3] Radiotherapy is the primary modality of treatment in head and neck cancers, as organ preservation is the major goal, but the fact that local recurrence is a major cause of failure has led to a number of studies to investigate the role of dose intensification of radiation in head and neck cancers.[4]

The conventional system of fractionation i.e. 60-70 Gy in 2 Gy per fraction five times a week as the optimal way of delivering radiotherapy in all circumstances is highly debatable.[5] While treating head and neck cancers with radiation, a balance is to be maintained between four parameters i.e., total radiation dose, dose per fraction, overall treatment time and the irradiated volume.[6] One of the most important biological factors hindering the local control is accelerated repopulation of tumour cells after the initiation of treatment. Treatment with chemotherapy or radiation triggers the surviving cells in tumour to divide faster than before and a larger proportion of tumour clonogenic come to the replication pool.[7] This can make the tumour resistant to conventional fractionation of radiation as well as to chemotherapy .There are a number of clinical reports which prove that a decrease in treatment time has improved the clinical outcomes which is clinically and biologically documented.[8]

Shorter treatment time can be achieved by applying a higher dose per fraction which may increase the rate of complications disproportionately .Hence the number of fractions delivered per week is increased without increasing the dose per fractions.This fractionation is called accelerated radiotherapy i.e., 60-70 Gy in 2 Gy / fractions, six times a week, Monday to Saturday. Accelerated fractionation shortens overall treatments time, minimizes tumour repopulation during treatment and therefore increases the probability of tumour control for a similar total dose.[9]

In conventional fractionation radiotherapy, the patients were given a total dose of 60-70 Gy in 2 Gy / fractions, five times a week, Monday to Friday. The main aim was to assess whether similar disease control could be achieved with Accelerated Fractionation Radiotherapy (AFRT) as compared with Conventional Fractionation Radiotherapy (CFRT) in head and neck cancers in the Indian population.[10] The aim of the study was to assess the treatment response by locoregional control and radiation toxicity resulting from

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conventional and accelerated fractionation radiotherapy in squamous cell head and neck cancers.

MATERIAL AND METHODS

This was a prospective randomized study with the treatment of accelerated as well as conventional fractionation radiotherapy executed from June 2018 to September 2018. The eligibility[11] of the study population was based on some inclusion criteria like

1. Consent for treatment
2. Age less than 60 years
3. Good performance status
4. No comorbidity
5. Confirmed malignant histology
6. No prior treatment (surgery or neoadjuvant chemotherapy)
7. Normal hematological, renal and hepatic function tests
8. No evidence of distant metastases

The tumour sites include the oral cavity, Oropharynx, Hypopharynx and larynx .The tumour stages were confined to stages I-III. All patients had regional nodal metastases. About 25 patients were enrolled in each arm. The patients were randomly assorted into two arms.

ARM A – study group – AFRT – Received accelerated six fractions per week, Monday to Saturday, 2 Gy /day up to 66 Gy in 5.3 weeks.

ARM B – control group – CFRT – Received conventional five fractions per week, Monday to Friday, 2 Gy /day up to 66 Gy in 6.3 weeks.

The pretreatment evaluation protocol included

1. Detailed Clinical history
2. Complete physical examination
3. ENT Evaluation
4. Routine Blood test.
5. Chest X-ray
6. CT scan of Head and Neck
7. Dental Evaluation
8. HIV testing
9. Echocardiogram

During radiation treatment, the field of radiation included the gross primary tumour with a generous margin (2-3cm) with a bilateral neck.After 44 Gy, the posterior neck field was reduced to spare spinal cord .All the patients were treated in Tele Cobalt Machine. Mostly opposing lateral fields were used. During treatment adequate nutritional support, aggressive hydration, antiemetic therapy and psychological support were given.All patients were encouraged to complete the full treatment schedule in the allotted time period. some patients had minor interruption due to toxicity .Common radiation-induced toxicities encountered were anemia, mucositis, skin reactions, dysphagia, which were managed with intensive care.

The patients were assessed for locoregional disease response and radiation toxicities weekly during radiotherapy and at the end of treatment. The locoregional response was considered to be complete if there was complete regression of the disease with no visible or palpable disease, partial, if there was more than 50% regression in the lesion, stable, if lesion regressed less than 50% and progressive, if lesion increased by 25% or appearance of new lesion.During the course of radiation execution, tolerance to treatment was assessed by weight, performance status, and radiation reactions. The radiation toxicity was assessed according to RTOG (Radiation Therapy Oncology Group) toxicity criteria.

RESULTS

Twenty-five patients were recruited in both arms (table-1). In each arm, patients could not complete treatment because of discontinuation of treatment, radiation intolerance and stoppage of the radiation treatment. In the end, a total of 22 patients were available for analysis in both the arms. Table-2 shows the site of the tumour. All recruited patients were male (table-3). At the end of treatment, a complete response was identified in 78% of patients in Accelerated fractionation group (arm A) and in 72% of patients in conventional fractionation arm. (Figure 1) The onset of dysphagia was earlier in arm A, although the severity of dysphagia was the same by the end of treatment. There was no difference noted in using **NG** tube insertions because of dysphagia during treatment. (Figure 2) During treatment, patients in arm A found difficult to complete the treatment compared to

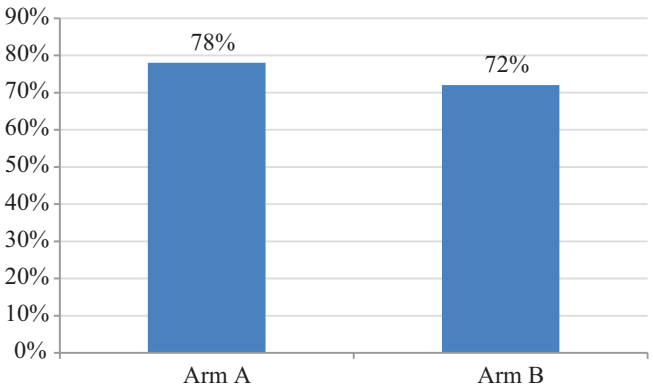

Figure-1: Complete response immediately after end of the treatment

Patients	Arm A	Arm B
Patients entered	25	25
Ineligible	3	3
Analyzable	22	22

Table-1: study population

Primary tumour site	Arm A	Arm B
Oral cavity	5	6
Oropharynx	8	9
Hypopharynx	7	4
Larynx	2	3

Table-2: Tumour site

	Arm A	Arm B
Age (Mean Year)	54.2	55.6
Sex	All Male	All Male
Performance Status	0-2	0-2

Table-3: Clinical characteristics

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	Loss of appetite	Decreased oral intake	Inadequate fluid and inadequate tube feeding	Intensive care
Vomiting	1-2 episodes in 24 hours	3-5 episodes	>6 episodes	Intensive care
Oral Mucositis	Minimal symptoms	Moderate pain	Severe pain interfering with oral intake	Intensive care
Skin	Discoloration	Hyperpigmentation with peeling	Ulceration	Intensive care
Anemia	hb <10 g%	8.0 -9.99 g%	6.5 -7.9G%	Intensive care
Febrile Neutropenia	count 1500	1000-1400	500-900	<500
Thrombocytopemia	count 7500	50000-74000	25000-49000	<25000

Table-4: Toxicity criteria and grading

Toxicity	Arm A	Arm B
Nausea	17	14
Vomiting	9	9
Mucositis	15	12
Dysphagia	14	8
Anemia	8	5
Neutropenia	5	3
Skin	22	18

Table-5: Toxicity

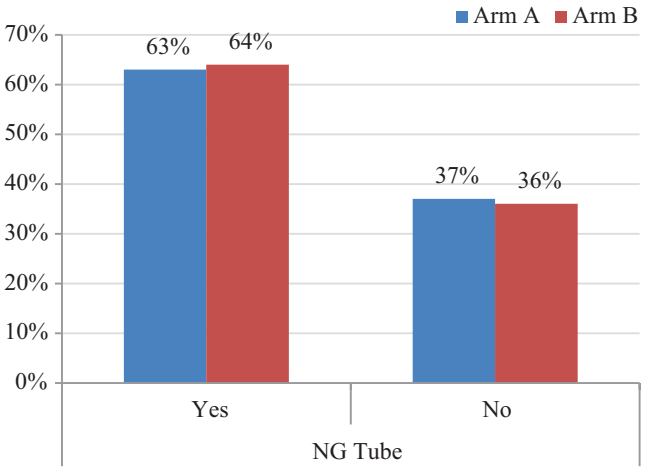

Figure-2: NG tube insertions because of dysphagia during treatment

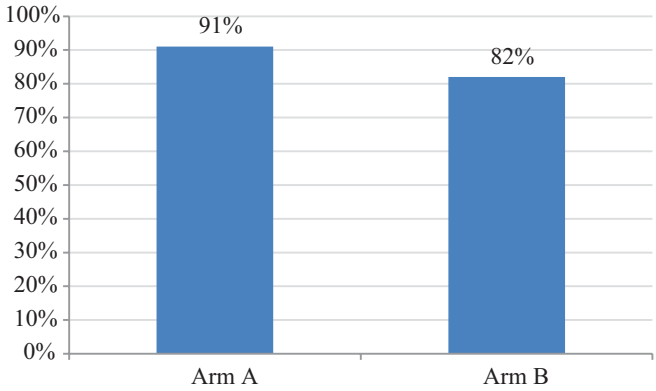

Figure-3: Grade 3 skin toxicity developed during treatment

arm B because of the higher incidence of radiation toxicity. Acute skin reactions were observed in both arms which were slightly more in arm A. (Figure 3) Acute mucositis was the most important toxicity observed in both arms and appeared early in the accelerated fractionation arm. Anemia and Neutropenia were encountered in both arms. The toxicities were treated intensively with intravenous fluids, blood transfusion, colony-stimulating factors, antibiotics etc. All the patients were given psychological support and were encouraged to complete the treatment without increasing the treatment period. (Table 4 and 5)

DISCUSSION

Head and neck squamous cell carcinomas are notorious for accelerated repopulation during the course of RT. This phenomenon usually sets in after four weeks of radiation therapy and to counteract this, 0.6 Gy of extra dose per day is needed.[11] To increase local control and survival, in the past decade, altered fractionation regimens have been assessed for the treatment of head and neck squamous cell carcinomas. The most commonly used altered fractionation schedules for the RT of advanced head and neck cancers are: Hyperfractionated RT to exploit the differences in radiosensitivity of cancer and normal cells in order to increase the therapeutic ratio; Accelerated RT to overcome tumour repopulation; Accelerated-hyperfractionated RT to combine the effects of the two irradiation regimens.

Several prospective randomized studies have shown that accelerated RT improves locoregional control in squamous cell carcinoma of head and neck. But accelerated regimens have been shown to increase treatment-associated acute morbidity, which in severe cases might lead to an increase in late radiation effects. This study was conducted with the objective that, pure accelerated RT with concomitant chemotherapy would result in better treatment outcomes compared to conventional chemoradiotherapy. Another objective was to find out whether patients can tolerate the new accelerated schedule.

In a prospective study by Gupta M et al.,[12] at first follow-up, 90.9% had a complete response at the primary site and 89.1% had a complete response at the nodal site in the accelerated arm and in conventional RT arm corresponding figures were 81.5% and 75.9%, respectively. At a median follow-up of 43 months CR was seen in 29 patients (52.7%) in the accelerated RT arm and 24 patients (44.4%) in the conventional RT arm. Though the difference in locoregional control was not statistically significant but this study clearly indicates a trend

towards the improved outcome. In Danish Head and Neck Cancer Study Group (DAHANCA) study,[13] loco-regional tumour control improved significantly in the accelerated fractionation group compared with that in the conventional RT group (70% vs. 60% five years actuarial rate, p=0.0005). There was 10% statistically significant improvement in locoregional disease control in the accelerated arm. In International Atomic Energy Agency (IAEA)-ACC study by Overgaard J et al.,[14] the five-year actuarial locoregional control was 42% in the accelerated versus 30% in the conventional group (p=0.004).

Limitations of the study

The sample size was minimal.

Head and neck cancer management is a field of multidisciplinary approach including oncology, ENT, plastic surgery, psychiatry etc. Hence during treatment, decisions had to be taken randomly at times.

As highly conformal radiotherapy was not given with higher machines like a linear accelerator, the surrounding organs were also damaged and a high dose of radiotherapy could not be delivered to the tumour bed in deserving patients.

CONCLUSION

To conclude, that accelerated six fractions per week treatment is a very feasible option and a better choice of radiation treatment in squamous cell Head and Neck cancers, especially in developing countries like India, were people work six days in a week.

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