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Original Research Article

Comparison of altered fractionation schedule with concurrent chemo-radiation for squamous cell carcinoma of head and neck

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ABSTRACT

Background: Aim of the study was to compare the response of altered fractionation schedule with concurrent chemo-radiation in patients with primary and the nodal disease.
Methods: Total of 40 patients (20 in each arm) with stage 1- 4 squamous cell carcinoma of the head and neck with a performance status of 0-2 (ECOG) were included in the study. Arm A was altered fractionation schedule where in patients received 6 fractions per week to a total dose of 6600 cGy in 33 fractions. In Arm B, patients received conventional radiotherapy with concurrent chemotherapy three weekly Inj. of cisplatin (100 mg/m^2). Patients were evaluated for acute toxicity every week using the Acute Radiation Morbidity Scoring Criteria. The response was assessed after 6 weeks and 12 weeks post treatment using the RECIST criteria. Data was statistically analyzed.
Results: Seventeen patients in Arm A and 18 patients in Arm B completed the treatment. At the end of three months, In Arm A, 7 patients had complete response and in Arm B, 9 patients had complete response of the primary ($p>0.05$). When the complete nodal response was compared in both the arms, there was no difference (2 vs 4 in Arm A vs Arm B resp.). But there were more partial nodal responders in Arm B ($p = 0.016$). The acute toxicities were comparable in both the arms.
Conclusions: Altered fraction radiotherapy can be used in early lesions with minimal nodal burden but with locally advanced disease or large nodal burden addition of chemotherapy should not be avoided.

Keywords: Acute toxicity, Altered fractionation, Concurrent chemo-radiation, Radiotherapy, Squamous cell carcinoma of head and neck

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is a locoregional disease confined to the primary tumor and the regional lymph nodes; distant metastasis is rarely seen at the time of diagnosis. Radiotherapy and surgery are thus the treatment of choice with Radiation therapy (RT) playing a pivotal role in the treatment management of HNSCC, if organ preservation is required. Over the past 2 decades, there have been several major advances in the treatment of cancers of the head and neck. Accelerated RT applied to squamous cell carcinoma of the head and neck yields better loco-regional control than does a conventional schedule with identical dose and fractionation. This is in agreement with several similar but small randomized studies.[1-5] Effective chemotherapeutic agents have been developed for HNSCC and are increasingly used sequentially or concurrently with radiation to treat unresectable cases or to promote organ preservation.[6-9]

In curative intent radiotherapy of HNSCC, besides tumor-related prognostic factors, differences in clinical outcome could be accounted for by the addition of chemotherapy. The addition of chemotherapy to radiation helps to sensitize tumors by inhibiting the repair of sublethal radiation damage and preferentially killing hypoxic cells. Concurrent chemo-radiotherapy (CTRT) has shown to improve loco-regional control and has become the standard of care for locally advanced HNSCC. The benefit in terms of locoregional control and survival, in altered fractionation, led many investigators to evaluate concurrent CTRT versus altered fractionation. The altered fractionation schedules have been compared with definitive radiotherapy alone which was the standard of care earlier, but there are no studies comparing altered fractionation schedule with concurrent chemo radiotherapy arm. Hence, this study was aimed to compare the locoregional response of altered fractionation schedule with concurrent chemo-radiation and its acute toxicities in patients with locally advanced head and neck cancers.

METHODS

Study design and sampling

A descriptive comparative study was conducted during two year period in the Department of Radiation Oncology, Vydehi Institute of Medical Sciences, Bengaluru, Karnataka. Patients with histologically proven HNSCC visiting the department for a period of 2 years were taken up for the study after obtaining the ethical committee approval. Patients were included in the study, based on the previous year's hospital records. Inclusion criteria were histologically proven HNSCC considered suitable for curative treatment, staging according to AJCC 7th edition, age 18 - 70 years, ECOG performance status 0-2. Patients with metastatic disease, previous radiation therapy, previous or planned surgical excision of the primary or lymph nodes, nasopharyngeal carcinoma or stage I glottic carcinoma were excluded from the study.

Study procedure

Forty patients were included in the study, twenty in each arm. All patients underwent 3D conformal planning. Arm A: Altered fractionated schedule (6600cGy in 33fraction, 6 fractions per week). Arm B: Concurrent chemo radiation schedule (7000cGy in 35 fractions, 5 fractions per week with three weekly Inj. of cisplatin 100 mg/m^2). Radiotherapy was delivered using the shrinking field technique with two opposing lateral fields and one lower anterior neck followed by an off-cord field to anterior neck and electrons to posterior neck. When assigned 6 fractions a week, all the patients received the 6th dose on Saturdays. In a few cases, the extra dose was provided on the last working day of the week with at least 6hrs between the two fractions. Plan analysis was done using dose volume histogram for target volume and normal structures.

Statistical analysis

Data were analyzed by Graph Pad In stat software (Version 3).The qualitative data comparison was done using Chi-square test while quatitative data was analysed using paired t test and p value less than or equal to 0.05 was considered statistically significant.

RESULTS

A total of 40 patients were included in the study. There were 30 male and 10 female patients. The patient and tumor characteristics were summarized in Table 1. Forty percent of the patients in arm A had larynx as primary site where as in arm B, 45% had oral cavity as primary site. Majority of patients in both the arms had T3 disease. 30% of patients in arm R had no nodal involvement. In arm B 70% of the patients had N2+ nodal disease.

Table 1: Gender and stage wise distribution of patients.

Characteristics		Arm A	Arm B
Subjects		20	20
Age (Mean±SD)		53.1±7.43	55.2±7.10
Sex	Male	17 (85%)	13 (65%)
	Female	3 (15%)	7 (35%)
Performance status	1	5 (25%)	6 (30%)
	2	15 (75%)	14 (70%)
Site			
Oral Cavity		6 (30%)	9 (45%)
Oropharynx		4 (20%0	6 (30%)
Larynx		8 (40%)	4 (20%)
Hypopharynx		2 (10%)	1 (5%)
Staging			
T Stage			
T2	2 (10%)		6 (30%)
T3	12 (60%)		10 (50%)
T4a	5 (25%)		3 (15%)
T4b	1 (5%0		1 (5%)
N Stage			
N0	6 (30%)		2 (10%)
N1	4 (20%)		4 (20%)
N2a	0 (0%)		2 (10%)
N2b	6 (30%)		7 (35%)
N2c	3 (15%)		5 (25%)
N3	1 (5%)		0 (0%)

Seventeen patients in arm A and 18 patients in arm B completed the planned treatment. Only 8 patients in arm A and 11 patients in arm B completed the treatment in time (6 weeks and 7weeks respectively). Only 2 patients in arm B received the planned 3 cycles of chemotherapy. 14 patients received 2 cycles and 2 patients could receive only 1 cycle (Table 2).

Table 2: Treatment characteristics of patients.

Treatment	Arm A		Arm B		Total
Completed	17 (85%)		18 (90%)		35
	≤6 weeks	8	≤7 weeks	11	19
	>6 weeks	9	>7 weeks	7	16
Incomplete	3 (15%)		2 (10%)		5

When the response was evaluated at the end of 6 week for the primary, 4 patients had complete response, 11 had partial response and 2 had stable disease in arm A where as in arm B 1 patient had complete response, 12 had partial response and 5 had stable disease (Table 3). Out of 11 patients with nodal disease in arm A, 2 had complete response, 3 had partial response and 6 had stable disease and in arm B out of 16 patients 1 had complete response, 12 had partial response and 3 had stable disease. The partial nodal response in both arms was statistically significant (p value- 0.04). There was no statistical difference in both the groups when primary response was compared. The response assessment at 3 months showed that there were 7 complete responders, 4 partial responders and 6 had disease progression in arm A when compared to 9 complete response, 6 partial response 3 progressive disease in arm B. When the nodal response was compared in both the arms, 2 patients showed complete response, 3 partial response and 6 progressive diseasein arm A and in arm B 4 had complete response, 11 had partial response and 1 had progressive disease. So at the end of 3 months 7 patients in arm A and 9 patients in arm B had complete response which was not statistically significant. When the nodal response was compared, there were 2 patients in arm A and 4 in arm B with complete response, but there were more partial responders in arm B (11 vs 3, p value - 0.016) which was statistically significant.

Table 3: Response to primary and nodes at 6 weeks and 3 months.

Response at 6 weeks	Arm A				Arm B				Chi- square test	p value
	SD	PR	CR	Total	SD	PR	CR	Total		
Primary disease	2	11	4	17	5	12	1	18	3.10	0.211
Nodal disease	6	3	2	11	3	12	1	16	6.04	0.004
Response at 3 months	**PR**	**CR**	**PD**	**Total**	**PR**	**CR**	**PD**	**Total**	**Chi- square test**	**p value**
Primary disease	4	7	6	17	6	9	3	18	1.62	0.44
Nodal disease	3	2	6	11	11	4	1	16	8.16	0.016

Grade 3 and 4 skin toxicity and mucosal toxicity was 25% and 55% vs 35% and 45% in arm A and arm B respectively (Table 4). In arm B 8 patients developed grade 3 and 4 hematological toxicities and 2 patients developed grade 3 and 4 GI toxicities. When acute toxicities were compared, there was no statistical difference in both the arms.

Table 4: Comparing major (Grade III and IV) toxicities in the two arms.

SITE	Arm A	Arm B	Chi-square	p value
Skin	5 (25%)	7 (35%)	0.47	0.49
Mucosa	11 (55%)	9 (45%)	0.4	0.52
Salivary gland	1 (5%)	1 (5%)	0.52	0.46
Pharynx	8 (40%)	6 (30%)	0.43	0.50
Larynx	2 (10%)	1 (5%)	0.36	0.54

DISCUSSION

Results of the study revealed that at the end of three months 7 patients in Arm A had complete response. While in Arm B, 9 patients had complete response of the primary. When the complete nodal response was compared in both the arms, there was no difference. Previous trials in which shorter treatment times were applied, though the total dose was reduced, a better or equivalent tumor response in the accelerated fractionation group was found.[10-13] Accelerated regimens, however, increase the treatment associated acute morbidity and if this effect becomes too severe it could increase the frequency of late radiation effects.[14] Similar findings have been noted in comparable studies, whereas in trials in which the acceleration was more prominent, late morbidity became unacceptable if the total dose was not reduced.[1,3,14] Thus, the window of opportunity for the benefit of acceleration is narrow and with the applied radiation technique a 1-week reduction seems to be the optimum balance between improved tumor control and avoidance of excess late morbidity.

The DAHANCA 6 and 7 study concluded that improvement in overall outcome with accelerated fractionation does not necessarily indicate that all patients would benefit equally from such treatment. The effect of acceleration they saw on locoregional control was entirely related to a better response in the T site, but did

not alter radiation effect on metastatic lymph node disease. Outcomes of patients in two treatment groups with large nodal burden and the locoregional control were substantially improved with 6 fractions per week. The corollary of this finding is a better effect of acceleration in laryngeal tumors, since these tumors have less nodal involvement than those in the pharynx and oral cavity. In this study also, patients with large nodal disease had poor response to altered fractionation when compared with the concurrent chemo-radiotherapy arm. However, there was no statistically significant difference in response at primary when both the arms were compared. In this study, treatment site did not affect treatment.

The histopathological differentiation of the tumor might affect the response to changes in overall treatment time. Thus, prolongation of the overall treatment time through split course radiotherapy especially decreased the outcome among patients who had moderately and well differentiated tumors, whereas poorly differentiated tumors were much less sensitive to variations in overall treatment time.[15] The reduction of the treatment time was, therefore, more beneficial in the moderately to well differentiated tumorsthat overall seems to be most sensitive to changes in treatment time. Similar dependency of differentiation and treatment time was noted in the CHART study.[16]

On the basis of these findings the hypothesis was formulated that the mechanism of repopulation in HNSCC is similar to the response in the normal mucosa from where the tumor has originated. Further studies are still needed to explore the mechanisms behind repopulation, which will hopefully consequently identify predictive factors to help improve treatment strategies and define targets for therapeutic intervention. The rate of acute radiation related morbidity was significantly higher in the accelerated fractionation group with a 53% frequency of confluent mucositis in DAHANCA study. Moreover, the mucositis persisted longer in the accelerated fractionation patients but all healed. In this study, the percentage of patients treated with altered fractionation schedule developing confluent mucositis was similar (55%). But it did not differ when compared with concurrent chemo-radiotherapy arm (45%). Some of the studies in the concurrent chemo arm used altered fractionation schedule. The results were better in concurrent chemo-radiotherapy arm. In some trials altered fractionation and chemotherapy have been combined to increase the local control. Though studies have shown benefit, but at the cost of severe morbidity and sometime mortality. The feasibility of such studies in Indian patients is doubtful. Both hyper fractionation and concomitant boost techniques have shown improved locoregional control but 6 fractions per week treatment can be preferred especially in developing countries with limited resources and acceptable toxicity. A randomized study is warranted to compare the altered fractionation schedule with concurrent chemo-radiotherapy.

CONCLUSION

This study concluded that the response to the primary in both arms did not show any statistically significant difference, but the partial nodal response in arm B was statistically significant which again ascertains the importance of concurrent chemotherapy with radiotherapy. The acute toxicity in both the arms was not statistically significant and the major toxicities encountered were treated symptomatically with good relief.

Based on this study, moderately accelerated radiotherapy could be used in early lesions with minimal nodal burden but with very advanced local disease or with a large nodal burden, addition of chemotherapy cannot be avoided.

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