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Original Research Article

COMPARATIVE ANALYSIS OF ALTERED FRACTIONATION WITH CONVENTIONAL FRACTIONATION IN CONCURRENT CHEMORADIATION OF HEAD AND NECK SQUAMOUS CELL CARCINOMA

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Abstract

Background: Head and Neck Squamous Cell Carcinoma (HNSCC) is a significant health concern in India. Treatment of locally advanced head and neck squamous cell carcinoma includes surgery, radiotherapy, and chemotherapy. Primary combined chemoradiation is also a standard of care for locally advanced head and neck cancers. **Aim:** This study aimed to compare the tumour response and acute toxicity of altered fractionation with conventional fractionation in Concurrent Chemoradiation of Head and Neck Squamous Cell Carcinoma (HNSCC). **Material & Methods:** A double-arm prospective randomised control study, in which 98 eligible patients with locally advanced HNSCC were randomised to altered fractionation (Study Arm – 55) receiving 55 Gy / 2.75 Gy / 20 fractions / 4 weeks and conventional fractionation (Control Arm – 43) receiving 66 Gy / 2 Gy / 33 fractions / 6 ½ weeks. Tumour response was evaluated using RECIST criteria 1.1 and acute toxicities based on the RTOG and CTCAE criteria 5.0. **Results:** The complete response rate was 63.6% and 41.9% in the study and control arms, respectively ($p = 0.03$). The incidence of acute dermatitis and mucositis (grade ≥ 3) in the study and control arms were 27.3% vs. 25.6%, with a p-value of 0.85 and 38.2% vs. 37.2%, respectively, which were insignificant ($p=0.92$). The patients in both arms were followed up to assess locoregional control, disease-free survival, recurrence rate, metastatic rate, overall survival rate and late toxicities. **Conclusion:** The altered fractioned regimen showed a tumour response comparable to conventional fractionation in locally advanced HNSCC, with increased but tolerable toxicities.

INTRODUCTION

Head and Neck Squamous Cell Carcinoma (HNSCC) is a major health problem in India, accounting for 30% of all cancers, with 70–80% occurring at an advanced stage. Locally advanced squamous cell carcinoma of the head and neck is treated using a combination of multiple modalities, including surgery, radiotherapy, and chemotherapy. Primary combined chemotherapy with cisplatin and radiation is the standard treatment for patients with locally advanced, unresectable tumours.[1,2]

The global incidence of malignancies affecting the head and neck region has surpassed half a million cases annually. In the United States, the incidence of new cases of head and neck cancer (HNC) was 40,500 in 2006, constituting approximately 3% of all adult malignancies. Nearly 60% of this population presents with locally advanced rather than metastatic disease. In India, HNCs primarily affect the oral cavity and pharynx. The age-adjusted incidence for these sites in Indian males ranges from 10.8 to 38.8 per 100,000 males, and for females, it is 6.4 to 14.9 per 100,000 females. Mouth and pharynx cancers rank as the third most common cancer in males and the fourth most common in females in developing countries. At the Institute Rotary Cancer Hospital, AIIMS, New Delhi, HNCs accounted for 25% of all newly registered cases. Oral cancer constitutes a significant health challenge in India, representing 50–70% of all diagnosed cancers, compared to 2–3% in the UK and the USA. The age-standardised incidence rate of HNC in males exceeds 30 per 100,000 in regions including France, Hong Kong, the Indian subcontinent, Central and

Eastern Europe, Spain, Italy, Brazil, and among US Blacks.[3,4]

Many randomised controlled trials have demonstrated improvements in locoregional tumour control from altered fractionation radiotherapy with or without chemotherapy, compared to conventional fractionation. Altered fractionation schedules improve the therapeutic ratio between tumour cell killing and normal tissue damage by exploiting the dissociation between acute and late radiation effects. High incidence rates of head and neck cancer (HNC) exceeding 10 per 100,000 are observed in females in the Indian subcontinent, Hong Kong, and the Philippines.[3] Most HNCs are linked to smoking, including carcinoma of the tongue, floor of the mouth, tonsil, base of the tongue, larynx, and pyriform sinus. However, cancers such as parotid malignancies, are not associated with smoking. HNCs exhibit local invasion of regional lymph nodes and typically remain confined to their site of origin and regional lymphatics. Locally advanced cancer indicates spread to nearby tissue or lymph nodes without distant metastasis.[3-5] The primary treatment modalities for HNCs are surgery, chemotherapy, and radiotherapy (RT). Although surgery and RT are predominant, concurrent chemotherapy and RT are the most effective approaches. Chemotherapy is particularly employed for metastatic cervical lymph nodes with an unknown primary tumour, carcinoma of the pyriform fossa and nasopharynx due to their high rate of lymph node metastasis.[5]

In RT, conventional fractionation in the United States involves a fractional dose of 1.8–2.0 Gy given once daily from Monday to Friday for the curative treatment of most cancers. A novel RT regimen, administering six fractions per week, has shown improved tumour control (76% vs. 64% for six and five fractions, respectively). The 6-day RT regimen demonstrates enhanced locoregional control with a median overall treatment time of 40 days compared to 47 days in the five-fraction group, presenting a significant advantage, especially in developing countries like India.[6]

Aim

This study aimed to compare the tumour response and acute toxicity of altered fractionation with conventional fractionation in locally advanced head and neck squamous cell carcinoma with concurrent cisplatin.

MATERIALS AND METHODS

This double-arm prospective randomised control study was conducted for one year, from August 2017 to July 2018. 98 newly diagnosed, histopathologically proven, locally advanced HNSCC patients were recruited based on the inclusion and exclusion criteria. Eligible patients were randomised using simple randomisation to concurrent chemoradiotherapy with either altered fractionation (Study Arm–55) or conventional fractionation (Control Arm–43). This study was approved by the Institutional Ethical Committee as per the standards of the WMA (World Medical Association) Declaration of Helsinki.

Written informed consent in the local language was obtained from all participants before the study. The location, size, and extent of the primary tumour and cervical lymph nodes were assessed using computed tomography scan (CT). Staging was performed according to the 8th edition of the American Joint Committee on Cancer TNM (AJCC TNM) 2018 staging system.

Inclusion Criteria

The inclusion criteria were biopsy-proven newly diagnosed locally advanced [stage III, IVA, IV B] Squamous Cell Carcinoma of the head and neck in the age group of 18-65 years with Karnofsky's performance status of >60%, primarily involving the oral cavity, oropharynx, hypopharynx, larynx with no evidence of distant metastases, and no major life-threatening comorbidities. The blood parameters were within normal limits (haemoglobin > 10 g%, Total WBC count >4000/mm3, Platelets >1,00,000 cells/mm3).

Exclusion Criteria

The exclusion criteria were non-squamous histopathology, tumours of other head and neck sites, deranged hepatic and renal functions (more than twice the upper limit) and reduced bone marrow reserve, no cooperation at any point in the treatment, pregnancy and lactation, metastasis, recurrence, or a history of previous irradiation.

Complete pretreatment evaluation with history and clinical examination, a biopsy from a tumour, weekly complete blood count, blood grouping and typing, liver function tests, renal function tests, and serum electrolytes before every cycle of chemotherapy, viral markers, CECT scan neck (from base of skull to Root of Neck), chest X-ray – PA view, ECG, Cardiology evaluation with fitness, pretreatment dental evaluation with prophylaxis, and audiological examination were performed.

Eligible patients in both arms were immobilised using thermoplastic moulds with suitable headrests and treated in Telecobalt using two parallel opposing fields. In the study arm, altered fractionation radiotherapy is delivered in the form of Phase I to include the primary and the draining lymph node regions to a dose of 41.25 Gy in 15 fractions over three weeks, followed by Phase II with off-cord reduction to a dose of 13.75 Gy in 5 fractions over 1week at 2.75 Gy per fraction is delivered five days in a week (Monday to Friday) to a total dose of 55 Gy in 4 weeks. In the control arm, conventional radiotherapy was delivered in the form of Phase I to include the primary and draining lymph node regions to a dose of 40 Gy in 20 fractions over four weeks, followed by Phase II with off-cord reduction to a dose of 26 Gy in 13 fractions over 2 ½ weeks at 2 Gy per fraction, which was

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delivered five days in a week (Monday to Friday) to a total dose of 66 Gy in 6 ½ weeks.

In both arms, all patients received chemotherapy, Inj Cisplatin (100 mg/m2) was administered in divided doses over three days from day 1 of RT with proper premedication was given every three weeks for a total of three cycles. Care was taken to maintain adequate hydration, nutrition, and analgesia before, during, and after the completion of treatment. In case of deranged blood parameters or any severe grade 3 or 4 toxicities, treatment was interrupted until recovery and then restarted. The patients were carefully monitored for toxicities, and supportive care was provided as needed.

All patients in both arms were assessed with a CECT Scan two months after completing chemoradiation to evaluate the locoregional response and were categorised according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria (version 1.1). Acute toxicities were assessed from the start of chemoradiation based on (Radiation Therapy Oncology Group (RTOG) acute morbidity criteria and CTCAE (Common Terminology Criteria for Adverse Events) version 5.0.

Statistical Analysis

The various parameters were analysed using SPSS Statistics 21.0. Chi-square tests were used to compare variables.

RESULTS

Ninety-eight eligible patients were recruited and randomised into the study arm (55) and the control arm (43). The variables analysed are shown in Table 1. [Table 1]

Of the 55 patients in the study arm, 30(54.5%) were male and 25(45.5%) were female, similar to the control arm; of the 43 patients, 23(53.5%) were male and 20(46.5%) were female, with a male: female sex ratio of 1:1 in both arms. The mean ages of the study and control arms were 52 (35–76 years) and 51 (37–74) years, respectively. The proportion of patients in varying age groups of <40, 40 -60 and >60 years in both the study and control arms was 11%, 60%, and 29% and 7%, 58%, and 35%, respectively, with a majority in the age group of 40-60 years in both arms.

The proportions of patients with primary tumour sites in the oral cavity, oropharynx, hypopharynx, and larynx in both the study and control arms were 34.5%, 20%, 23.5%, and 22%, and 35%, 21%, 25%, and 19%, respectively. The stage at presentation {Stage III, IVA and IVB} in the study and control arms was 31%, 53%, and 16%, and 30%, 56%, and 14%, respectively, with the majority being Stage IVA disease in both arms.

In the study arm, out of 55 patients, 35 (63.6%) achieved complete response (CR), 17 (31%) achieved partial response (PR), and 3 (5.4%) had stable disease (SD) compared to the control arm, with 43 patients, 18 (41.9%), 20 (46.5%), 2(4.7%), and 3 (6.9%) patients having CR, PR, progressive disease, and SD, respectively. No patient with disease progression was observed in the study arm. There was a significant increase in the complete response rate in the study arm compared to that in the control arm ($p = 0.032$).

The incidence of acute dermatitis in grades 1 and 2 and grades 3 and 4 in the study and control arms was 72.7% vs. 74.4% and 27.3% vs. 25.6%, respectively ($p = 0.85$). The incidence of acute mucositis in grades 1 and 2 and grades 3 and 4 in the study and control arms was 61.8% vs. 62.8% and 38.2% vs. 37.2%, respectively ($p = 0.92$). Xerostomia, anorexia, nausea, vomiting, diarrhoea, and fatigue were other treatment-related toxicities in both groups. The patients in both arms were followed up to assess late toxicities, locoregional control rates, disease-free survival, and overall survival.

Table 1: Comparative analysis of study and control arm variables

Variables		Study Arm (n)	Control Arm (n)
Sex	Male	30	23
	Female	25	20
Age (in Years)	<40	6	3
	40- 60	33	25
	>60	16	15
Primary Tumour Site	Oral Cavity	19	15
	Oropharynx	11	9
	Hypopharynx	13	11
	Larynx	12	8
Stage	III	17	13
	IV A	29	24
	IV B	9	6
Clinical Response	Complete	35	18
	Partial	17	20
	Progressive	Nil	2
	Static	3	3
Acute Toxicity			
Dermatitis	Grade 1 & 2	40	32
	Grade 3 & 4	15	11
Mucositis	Grade 1 & 2	34	27
	Grade 3 & 4	21	16

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DISCUSSION

Hypofractionated radiotherapy utilises a small number of fractions with a larger dose per fraction, shortening the overall treatment time compared to a conventional protocol. Although 2.0 Gy fraction size has been considered standard, modest, and daily hypofractionation with fractional doses between 2.5 and 3.3 Gy has been common practice in countries such as the United Kingdom and Canada, where a reduction in total treatment time represents significant cost savings. Long-term data were available from multiple randomised hypo-fractionated trials.[7]

The influence of fraction size on radiation therapy outcome manifests through the slope of fractionated dose-response curves, which reflects the cellular repair capacity. However, hypofractionation schedules may increase the incidence of late complications. Although most centres adopt the conventional 2 Gray (Gy)/fraction schedule, a substantial proportion of patients in the United Kingdom (UK) receive a hypofractionated prescription with larger doses per fraction, such as 55 Gy in 20 fractions (2.75 Gy/fraction). This regimen has the theoretical advantage of completing the treatment before accelerated tumour cell repopulation becomes a significant factor.[8,9]

Shangera et al. studied 81 patients with squamous cell cancer of the larynx, oropharynx, oral cavity, and hypopharynx who received hypo-fractionated radiotherapy at a dose of 55 Gy in 20 fractions with concurrent chemotherapy. The 2-year local control rate was 75.4%. The 2-year OS and disease-free survival rates were 71.6%, and 68.6%, respectively.[10]

This double-arm prospective randomised controlled trial compared the altered fractionated regimen with conventional fractionation radiotherapy along with concurrent chemotherapy for locally advanced HNSCC. The altered fractionation showed a better clinical complete response, with a significant p-value of 0.032, compared to the control arm. The incidence of treatment-related acute toxicities was higher in the study arm than in the control arm. Still, it was insignificant, with p-values of 0.85 and 0.92 for dermatitis and mucositis, respectively.[11]

Hypofractionation is an alternative to conventional regimens with a shorter treatment time but with concerns about late toxicities. Its development should not occur at the expense of decreased locoregional control or unacceptable late toxicity.[12]

The comparison between concomitant chemoradiotherapy and altered fractionation has yet to be conducted, and currently, there is no indication that one treatment is superior to the other. The difference in overall survival at five years in favour of altered fractionation in this meta-analysis was 8.1%, which is very close to the overall survival results reported in the most recent update of the MACH-NC meta-analysis (6.5%) for concomitant chemotherapy plus radiotherapy.[2]

Previous research has also indicated that mucous membranes are the most common site of severe acute reactions, and in some studies, mucositis was identified as the dose-limiting toxicity.[13,14]

Our understanding of the effects of radiation on crucial cellular processes and DNA repair mechanisms is based largely on conventional fractionation. Significant differences in the gene expression response patterns may result from various forms of altered fractionation. Further investigation into these differences may reveal targetable pathways to enhance tumour response to fractionated radiotherapy. Molecular profiling of tumours in preclinical studies has revealed an array of targetable molecules (such as NF-κB and STAT1) that vary with dose and fractionation. Advances in understanding molecular biology, immunotherapy, and genomics have opened exciting possibilities and broadened our ability to identify subgroups of tumours that best respond and patients who will best tolerate altered fractionation.[15]

Patients with complete responses were regularly followed up. However, those with PR, progressive disease, or SD were further evaluated and referred to a surgical or medical oncologist for further management. All patients in both arms were treated with a telecobalt machine using a conventional technique. If higher IMRT or Rapid Arc techniques using LINAC are used, a better toxicity profile can still be achieved in both arms. Further, a longer follow-up period is needed to assess the patients' locoregional control, disease-free survival, recurrence rate, metastatic rate, overall survival rate, and late toxicities.

CONCLUSION

The altered fractioned regimen showed a comparable tumour response to conventional fractionation in locally advanced HNSCC, with increased but tolerable toxicities. It has the theoretical advantage that treatment is completed before accelerated tumour cell repopulation becomes a significant factor. Reducing the number of fractions and treatment time allows for more efficient use of resources, avoiding prolonged treatment periods and long waiting times in busy centres.

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