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Research Article

TREATMENT OUTCOME AND TOXICITY OF HYPOFRACTIONATED RADIOTHERAPY WITH CONCOMITANT CHEMOTHERAPY VERSUS CONVENTIONAL FRACTIONATED CONCOMITANT CHEMORADIATION IN LOCALLY ADVANCED HEAD-AND-NECK CARCINOMA: A COMPARATIVE STUDY

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ABSTRACT

Objectives: In our study, radiation of a higher dose per fraction (2.75 Gy/fraction, total dose of 55 Gy/20 fractions/4 weeks) with concomitant chemotherapy was compared with conventional chemoradiation (2 Gy/fraction, a total dose of 66 Gy/33 fractions/6 and half weeks, with concomitant chemotherapy), in patients of locally advanced squamous cell carcinomas of head and neck in terms of efficacy and toxicities.

Methods: A total of 75 patients registered at the Department of Radiotherapy, NRS Medical College and Hospital, Kolkata, were allotted in two arms chronologically in a 1:1 ratio. Arm A – Patients received hypofractionated radiotherapy, 55 Gy/20 fractions in 4 weeks with concomitant weekly cisplatin (40 mg/m^2). Arm B – Patients received conventional radiotherapy, 66 Gy/33 fractions in 6½ weeks with concomitant weekly cisplatin (40 mg/m^2).

Results: Both in terms of efficacy and toxicities, the hypofractionation arm was comparable to the conventional arm, and no statistically significant difference was present between the arms. For the study arm, complete response was 56.6%, partial response was 36.6%, and for control arm, complete response 50% and partial response 37.5% (p=0.750). In terms of acute toxicities and late dysphagia, both the arms were almost similar.

Conclusion: The hypofractionated regimen was associated with tolerable acute and late toxicities and satisfactory local control. Considering the patient load, the overall treatment time, and the cost of hospital stay, this hypofractionated regimen is a good treatment option in our low-resource setup.

Keywords: Hypofractionation, Head-and-neck cancer, Chemoradiation.

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INTRODUCTION

Head-and-neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide [1]. The incidence of head-neck cancers varies widely around the world and even within different populations. Oral and oropharyngeal cancer constitutes 3–5% of malignancies in Europe, while this figure in parts of Southeast Asia and India reaches up to 40–50% [2-4]. Approximately 60% of patients with HNSCC present with locally advanced, but the non-metastatic disease (Stage-III or IVA) at diagnosis and based on organ preservation studies [5-8,]. The recent research in fractionation is in the opposite direction wherein a renewed interest in a dose per fraction much larger than 2 Gy for curative radiotherapy.

The results of many large fractionation trials, mainly involving head-and-neck tumors, and particularly the CHART trial, have demonstrated the advantage of "acceleration," that is, shortening the overall treatment time to improve local control [9]. On the other hand, because of the long repair half-times of late reacting normal tissues, the usefulness of using multiple treatments (fractions) per day is limited in situations like India, where many patients are waiting for treatment [10,11]. Instead, the alternative strategy uses a smaller number of once-daily larger dose fractions.

Accelerated RT, that is, increasing the dose above the standard 10 Gy per week to shorten the overall treatment time, has been shown in many randomized controlled trials [12,13] to be associated with an improved efficacy to toxicity ratio (therapeutic ratio) relative to standard fractionation. This accelerated RT provides a careful balance between total dose, dose per fraction, and overall treatment time. One of the most important lessons from fractionation studies is that local control is lost when the overall treatment time is prolonged. For head-and-neck cancer, in particular, local control is reduced by 0.4–2.5% for each day that the overall treatment time is prolonged [14,15]. In other words, after the first 4 weeks of a fractionated schedule when the accelerated repopulation starts, the first 0.61 Gy of each day's dose fraction is required to overcome the proliferation of the previous day. In hypofractionated radiotherapy, a small number of fractions are given with a greater dose per fraction thus resulting in shortened overall treatment time compared to a conventional protocol. In the UK, a substantial number of patients receive a hypofractionated prescription with larger doses per fraction, such as 55 Gy in 20 fractions (2.75 Gy/fraction) [16,17]. The attractive feature of this approach is that the total treatment time is shorter than the conventional treatment (4 vs. 7 weeks in this case), thus being convenient for the patient, and the department can increase the number of treated patients with the same workload.

Prospective trials have also shown that chemotherapy given concurrently with radiotherapy (RT) enhances locoregional control and overall survival compared with RT alone [18-23]. Chemotherapy-induced radiosensitization can, therefore, be considered a method of biological dose escalation [24] and there is an average gain of about 3.6 fractions of 2 Gy/fraction for the effect of chemotherapy in head-and-neck radiotherapy [25].

METHODS

After obtaining ethical clearance for doing this research work from the Institutional Ethics Committee, biopsy-proved patients of LAHNSCC patients registered at the Department of Radiotherapy, NRS Medical College and Hospital, Kolkata, were allotted in two arms chronologically

in a 1:1 ratio. Arm A (study arm) – Patients received hypofractionated radiotherapy, 55 Gy/20 fractions in 4 weeks with concomitant weekly cisplatin (40 mg/m^2). Arm B (control arm) – Patients received conventional radiotherapy, 66 Gy/33 fractions in 6½ weeks with concomitant weekly cisplatin (40 mg/m^2). Data related to all study variables were collected precisely and recorded accurately in a prospective manner. Response assessment as per RECIST criteria version 1.1 (CR, PR, SD, PD) was assessed after 12 weeks of completion of treatment, and the disease (tumor control) status was assessed at the end of the study period. Toxicities developed during and after treatment, were assessed by using the CTCAE scoring system. All statistical analyses were done by standard statistical test applicable using Microsoft and SPSS version 25.

Detailed radiotherapy technique

CT-based simulation

Contrast-enhanced planning CT scan was done in SIEMENS Ltd. SOMATOM EMOTION 16 computed tomography machines. Patients with a history of allergy to contrast agents were scanned without contrast. Planning CT scan was taken in supine position with arms beside the body, head extended. Immobilization was done with five clamps thermoplastic head-and-neck mold with base plate and headrest as required. The reference line was made using radio-opaque balls. All patients were scanned from vertex to mid thorax with 2.5 mm sections. The images so obtained were reconstructed three-dimensionally by the system and were transferred to the VARIAN planning system.

Target volume and organ at risk delineation

Contouring was done with Varian Eclipse (version 15.1) treatment planning system.

- GTV (gross tumor volume) includes all gross primary tumors and involved lymph node(s) as determined by physical, pathological examination, and imaging.
- CTV (clinical target volume): Volume that contains GTV and/or subclinical microscopic malignant disease.

In the present study, the CTV had been divided into three groups:
CTV-High: GTV+1.0 cm

- CTV-Intermediate: Remaining area at high or intermediate risk of involvement which included the adjacent nodal levels.
- CTV-Low: Low-risk nodal levels.

PTV (planning target volume): The PTV is defined by specifying the margins that must be added around the CTV to manage the effects of organ, tumor, and patient movements, inaccuracies in beam and patient setup, and any other uncertainties. The PTV is a static, geometrical concept used for treatment planning and specification of dose. In the present study, PTV= CTV+0.5 cm

- OAR (an organ at risk) – The critical normal structures delineated included parotid gland (right and left), spinal cord, spinal cord, mandible, cervical esophagus, brain stem, optic nerve (right and left), optic chiasm, cochlea (right and left), larynx, eyeball (right and left), and lens (right and left).
- PRV (planning organ at risk volume) – 3 mm margin was applied around OARs

Dose

ARM A (study/hypofractionated ARM).

55 Gy in 20 fractions (#) over 4 weeks with 2.75 Gy/fraction,

- CTV-HIGH (high-risk CTV) – 55 Gy in 20#
- CTV-INTERMEDIATE (intermediate-risk CTV) – 49.5 Gy in 18#
- CTV-LOW (low-risk CTV) – 46.75 Gy in 17#.

ARM B (control/conventional ARM).

66 Gy in 33 fractions (#) over 6.5 weeks with 2 Gy/fraction

- CTV-HIGH (high-risk CTV) – 66 Gy in 33#
- CTV-INTERMEDIATE (intermediate-risk CTV) – 60 Gy in 30#
- CTV-LOW (low-risk CTV) – 50 Gy in 25#.

RESULTS

A total of 68 patients were evaluated for eligibility for the study. Among them, 65 were selected after fulfilling the eligibility criteria. They were allocated into two arms. One patient of each arm was excluded from analysis as the patient lost follow-up within the study period and one patient of the study arm died due to non-oncological complications. Hence, at the end of the study, only 62 patients were eligible for analysis with 30 patients in the study arm and 32 patients in the control arm. Baseline profiles of the patients in the arms were comparable in terms of age distribution, sex distribution, pre-treatment performance status, tumors (T) status, and nodal (N) status. A comparison of demographic profiles among different treatment arms showed no statistically significant difference, that is, all the profiles had p>0.05. Patients included in the study ranged from 40 to 70 years, mean age±standard error was 51.27±1.159 and 51.69±1.935 in hypofractionated and conventional arms, respectively, t-test showed that there was no significant difference in mean ages of the patients of the two groups (p=0.852). A total of 62 patients were included in the study out of which 45 were male and 17 were female. In the study arm, 22 males and eight females, and in the control arm, 23 males and nine females were present, Chi-square test showed that there was no significant association between gender and groups (p=0.614). The Chi-square test showed that the patients of the two groups were comparable in ECOG performance scores (p=0.59). The primary subsites of cancer were more or less equally distributed among the patients of the two groups (Chi-square p=0.40). The Chi-square test showed that the stages of cancer were more or less equally distributed among the patients of the two groups (p=0.585) (Table 1).

Tumor response

The proportion of patients with a complete response was almost the same for both arms. For the study arm, the complete response was 56.6% and the partial response was 36.6%, and for the control arm, complete response was 50% and the partial response was 37.5%. The Chi-square test showed that there was no significant difference in tumor response between the two groups (p=0.750) (Table 2).

Disease status in the last follow-up – In the study arm, 36.6% of patients had the detectable disease at the end of the study period whereas it was 37.5% of patients in the control arm, showing no significant difference in both arms (p=0.65) (Table 3).

Reactions observed between both the arms

The reactions were graded according to CTCAE version 4.03, analgesia using the WHO ladder pain scale, and treated appropriately during treatment. There were no significant (p=0.538) differences between the proportion of patients with oral mucositis in the two groups: For the study arm, Grade 3 toxicity 36.6% and, for the control arm, Grade 3 toxicity 37.5% (Chi-square p=0.538). In the study arm, skin reactions started at the end of the 2nd and beginning of the 3rd week whereas, in the control arm, skin reactions started at the beginning of the 3rd week, a peak was seen in the 5th and 6th week. There was no significant difference in skin toxicities between both arms (p=0.69). There was no statistically significant difference in hematological toxicities between the two arms. The Chi-square test showed (p=0.145) that there was no significant difference between the proportion of patients with anemia in the two groups. In the study arm, Grade 1 toxicity was 46.6% and, for the control arm, it was 71.8%. There was no significant difference between the proportion of patients with neutropenia in the two groups (p=0.655). In the case of thrombocytopenia also, both arms were comparable (p=0.593). Late toxicities, such as dysphagia and xerostomia, were observed in both arms. There was no significant difference in dysphagia (p=0.745). Although there was no statistically significant difference in xerostomia in both groups (p=0.066), the proportion of patients with Grade-1 xerostomia was a bit higher in the study group (83.3%) than that of the control group (62.5%) (Table 4).

DISCUSSION

We performed this study with 62 patients at a tertiary level hospital in Kolkata with a subsequent median follow-up of 1 year. The

Table 1: Distribution of baseline parameters

Arm	Sex distribution							
	Male	**Female**					**Total**	**p-value**
A	8	22					30	0.614
B	9	23					32	
Arm	**ECOG status**							
	0	**1**	**2**				**Total**	**p-value**
A	4	14	12				30	0.59
B	6	17	9				32	
Arm	**Primary site**							
	Oral cavity	**Oropharynx**	**Supraglottic larynx**	**Glottis**	**Subglottis**	**Hypopharynx**	**Total**	**p-value**
A	2	12	7	2	1	6	30	0.40
B	2	8	12	0	3	7	32	
Arm	**Disease stage**							
	III			**IVA**			**Total**	**p-value**
A	18			12			30	0.585
B	17			15			32	

Table 2: Response after treatment

Arm	Response				Total	p -value
	Complete response	**Partial response**	**Stable disease**	**Progressive disease**		
A	17	11	0	2	30	0.750
B	16	12	1	3	32	
Total	33	23	1	5	62	

Table 3: Disease status, at last follow-up

Arm	Disease status		Total	p-value
	Undetectable	**Detectable**		
A	19	11	30	0.65
B	20	12	32	
Total	39	23	62	

majority of our patients were in the range of 40–70 years age group with mean age±standard error of 51.27±1.159 and 51.69±1.935 in hypofractionated and conventional arms, respectively, which were similar to studies conducted by various authors [26,27]. In our study, patients with oropharyngeal, laryngeal, and hypopharyngeal cancers are more compared to other subsites which were similar to the study conducted by Staar *et al.* [26]. The majority of head-and-neck cancer patients usually present with locally advanced disease with 43.5% of patients presenting with a Stage IVA.

In our study, patients were treated with hypofractionation with weekly chemotherapy in the study arm with a radiotherapy schedule, 55 Gy in 20 fractions, 2.75 Gy/fraction, single fraction/day, and 5 fractions/week. We considered cisplatin, weekly 40 mg/m^2, 1 cycles/week during RT. Tumor and nodal delineation were done according to the guidelines [28-30]. The study regimen was comparable with the conventional regimen using the biologically effective dose described in the linear-quadratic model [18].

In our study, complete responses for the study and control arm were 56.6% and 50%, respectively, the partial response was 36.6% for the study arm and 37.5% for the control arm. Two cases of the study arm and three of the control arm had stable disease. Randomized control trials demonstrated that reducing the overall treatment time while maintaining the same dose and altered fractionation schedules, improved the 5-year local control by 10% [31]. Benghiat *et al.*, at Queen Elizabeth Hospital, Birmingham, UK, in the year 2014 measured the outcome of 4-week hypofractionated intensity-modulated radiotherapy (IMRT) (55 Gy in 20 fractions) and synchronous carboplatin in 85 Stages II-IV oropharyngeal cancer patients [32]. The 2-year LR-RFS was 68% for the whole cohort. Grade 3 mucositis was experienced by all patients who completed the planned 4 weeks of radiotherapy. There was no Grade 4 mucositis seen. Grade 3 skin reaction was observed in 36 patients (48%). Patients receiving concurrent cetuximab were significantly more likely to experience Grade 3 skin reactions versus those receiving carboplatin chemotherapy (p=0.002).

In another study, Chan *et al.* at the University of Warwick measured the outcome of hypofractionated RT with concurrent carboplatin for locally advanced HNSCC [33]. Hundred and fifty consecutive patients with squamous cell carcinoma of the larynx, oropharynx, oral cavity, and hypopharynx (Stages II–IV) were treated with 55 Gy in 20 fractions over 25 days with concurrent carboplatin [33]. There were 135 patients with Stages III and IV disease. For these patients, the local control and disease-free survival were 79.1% and 67.6%, respectively. Altered fractionation had shortened the overall treatment time, which was radiobiologically superior and beneficial where the patient load was more than the facility available for radiation and therefore recommended. In his study, overall response was 75% in hyperfractionation, 80% in accelerated fractionation, and 76% in conventional fractionation.

Roy *et al.* in the year 2015 at SSKM Hospital, Kolkata, compared hypofractionated versus conventional RT with or without chemotherapy in head-and-neck cancer (Stages 2–4b) [34]. The tumor response rate was comparable between hypofractionated RT versus conventional RT arm (80% vs. 75% of patients achieved a complete response) for oropharyngeal cancer subsites. Higher frequencies of acute Grade >2 skin toxicity, mucositis and late grade dysphagia, and xerostomia were encountered in the hypofractionated arm.

In our study, the tumor response was similar to Roy *et al.*, [34] with comparable toxicity. Overall, the incidence of Grade 3 oral mucositis was 36.6% in the study arm compared to the control arm (37.5%), the acute toxicities were manageable with treatment interruption of fewer than ≤3 days, and most of them healed within 3 months of the start of treatment. In our study, the incidence of higher Grade 3 skin reactions was less in both the arms with only two patients in the study arm and three patients in the control arm having Grade II dermatitis. The side effect profile was highly acceptable with no difference in long-term side effects and only a moderate increase in acute side effects that did

Table 4: Post-treatment toxicities

Toxicity	Arm	Nil	Grade I	Grade II	Grade III	Total	p-value
Acute mucosal	A	1	10	8	11	30	0.538
	B	1	6	13	12	32	
Acute skin	A	20	8	2		30	0.69
	B	18	10	3	1	32	
Anemia	A	11	14	4	1	30	0.145
	B	4	23	4	1	32	
Neutropenia	A	12	13	5		30	0.655
	B	10	14	8		32	
Thrombocytopenia	A	29	1			30	0.593
	B	30	2			32	
Late dysphagia	A	2	10	14	4	30	0.745
	B	2	15	12	3	32	
Xerostomia	A	5	25			30	0.066
	B	12	20			32	

not reduce compliance to treatment. RTOG 0522 results were similar to our study concerning acute toxicities. Long-term effects beyond the follow-up period were not studied [35]. In our study, Grade III dysphagia was noticed in 13.3% of the study arm and 9.3% of the control arm. All of these patients required nasogastric tube feeding and other supportive management. In our study, there was no statistically significant incidence of high-grade xerostomia in both arms of the study which was similar to the results of the prospective trials. In our study, hematological toxicity was comparable in both arms during treatment and also post-treatment with no treatment interruptions due to chemotherapy-related toxicities.

A follow-up of 1 year was done and the disease (tumor control) status was assessed. The detectable disease was proved using clinical and ENT examination, CECT face and neck and biopsy/FNAC were seen in 36.6% of patients of the study arm and 37.5% of patients of the control arm and were comparable in both arms. The ideal treatment combination was to choose optimal radiation fractionation with concurrent chemotherapy. Hypofractionation can be considered in LAHNSCC with weekly cisplatin, as it was well tolerated with improved locoregional control and comparable toxicity profile. The dose of 55 Gy in 20 fractions is based on a sound radiobiological basis as it has a similar log10 tumor cell kill as a schedule of 66 Gy in 33 fractions with the additional advantage of lower BED to late effect tissues (105·4 Gy3 vs. 110 Gy3) and a tolerable acute mucosal BED, as supported by the above discussed clinical trials and our study results. The 3DCRT seems to have added to this advantage by delivering more conformal dose distribution and better sparing of organs at risk. The highly conformal irradiation techniques like IMRT [35-37] with IGRT (adaptive radiotherapy) can further reduce toxicities and improve locoregional control when used in combination with altered fractionation and concurrent chemotherapy. The use of novel agents like targeted therapies may further increase tumor cell killing and ameliorate mucosal toxicity. However, the proper selection of a patient for treatment will also influence treatment outcome.

Study caveats: (1) Our sample size was small, so any statistical data have to interpret with caution. (2) It was a single-institutional study, hence, the results derived cannot be extrapolated to the entire population.

CONCLUSION

The present study using hypofractionated conformal radiation therapy in locally advanced head-and-neck squamous cell cancers was based on a strong radiobiological basis and also exploited the advantages of conformal treatment and concurrent chemotherapy. This hypofractionated regimen was associated with tolerable acute and late toxicities and satisfactory local control. This, concurrent chemoradiation in the form of hypofractionation with weekly cisplatin is a good treatment option in our country considering the patient load, the overall treatment time, and the cost of hospital stay. If the patients with locally advanced head-and-neck squamous cell carcinoma are treated, there will be a decrease in the cost of treatment, overall treatment time, and duration of hospital stay the patient. The number of patients treated will significantly increase which will decrease the waiting list of patients requiring treatment. However, to prove the exact benefit of hypofractionated fractionation, there is a need to perform large randomized studies with larger sample size, longer follow-up, to know the locoregional control, disease-free survival, disease site-specific survival, overall survival, and quality of life.

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AUTHORS' CONTRIBUTION

All authors contributed equally to this article including manuscript writing and reviewing statistical analysis.

CONFLICTS OF INTEREST

NIL.

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