

A comparison of outcomes with 'Christie Regimen' and pure accelerated radiotherapy versus conventional radiation in locally advanced squamous cell carcinoma of head and neck: A randomized controlled study

Krishnangshu Bhanja Choudhury, Shyam Sharma, Sumana Maiti, Chhaya Roy, Chandrani Mallick¹

Department of Radiotherapy, IPGMER and SSKM Hospital, Kolkata, ¹Burdwan Medical Hospital, Burdwan, West Bengal, India

ABSTRACT

Context and Aim: Radiotherapy is alternative to concurrent chemoradiation or surgery for locally advanced squamous cell carcinoma of head and neck (LAHNSCC) due to co-morbid conditions. The aim of this study was to compare efficacy and toxicity among hypofractionated, pure accelerated and conventional radiotherapy schedules. **Settings and Design:** Interventional randomized controlled study. **Materials and Methods:** Between May 2008 and May 2012, 132 LAHNSCC patients, AJCC stages III to IVB, creatinine clearance <60 ml/min, age more than 50 years, co-morbidities like uncontrolled diabetes, cardiac disease, ECOG 3 and 4, or combination of these were randomized into three arms: Arm A, "Christie Regimen", 50 Gray (Gy) in 16 fractions, 3.125 Gy per fraction over 3 weeks; Arm B, 66 Gy in 33 fractions in 6 fractions per week in 5.5 weeks; and Arm C, 66 Gy in 33 fractions, 5 fractions per week, in 6.5 weeks. The endpoints of the study were overall response (ORR = complete response + partial response), disease-free survival (DFS), toxicities, and overall survival (OS). **Statistical Analysis Used:** All statistical tests were done using ANOVA. OS and DFS were calculated using Kaplan–Meier analysis. **Result:** ORRs were comparable in all arms, P value = 0.401. DFS were in favor of altered radiation, P value = 0.034. Acute Grade 3 cutaneous toxicity (P value = 0.018) and mucositis (P value = 0.011) were high with altered fractionation. Chronic grade 2 and 3 toxicities were higher in altered fractionations. **Conclusion:** There was no difference in the ORR between three arms but DFS was in favor of altered fractionation arms with manageable toxicity. Both altered fractionation had short overall treatment time which is radiobiologically superior and is beneficial for centers like ours where the patient load is much higher than the facility available.

Key words: Christie regimen, conventional radiation, pure accelerated radiation

INTRODUCTION

Over one-third of all cancers in India occur in the head and neck. Nearly 60% of patients of head and neck cancer present with locally advanced but nonmetastatic disease.

Locoregional failure constitutes the predominant recurrence pattern. Results of treatment of these tumors are inversely proportional to the extent of the disease.

Squamous cell carcinoma of the head and neck is predominantly a locoregional disease, and the primary treatment methods are surgery and radiotherapy.^[1] Radiotherapy alone has long been the standard nonsurgical therapy for the locally advanced disease.^[2-4] The state of the art regarding radiation dose fractionation has evolved from once daily treatment to hyperfractionation and accelerated fractionation. Nonetheless, even the most effective radiation regimens result in local controls rates of 50% to 70% and disease-free survivals of 30% to 40%. These circumstances lead to the combined modality concurrent

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Address for correspondence: Dr. Shyam Sharma, Room No 104, Institute of Post Graduate Medical Education and Research and SSKM Hospital, 240, A.J.C Bose Road, P/S Bhowanipore, Kolkata - 700 020, West Bengal, India. E-mail: sharma.shyam123@gmail.com

chemoradiotherapy as the standard care of treatment for locally advanced head and neck cancer.^[5-7]

However, a significant number of patients with squamous cell carcinoma of the head and neck (HNSCC) are unsuitable for aggressive radical treatment with surgery or chemoradiotherapy (CRT) because of a very advanced locoregional disease, significant co-morbidities, poor performance status, distant metastatic disease, or a combination of these factors. However, this group of patients still requires some form of treatment to control their locoregional disease and to alleviate their troublesome symptoms.

The optimum treatment time for locoregional control is unclear. The possible cause for treatment resistance could be radiation-induced accelerated proliferation of clonogenic tumor cells. A reduction in the locoregional control by lengthening the treatment time has been clinically and biologically documented. Furthermore, in several clinical studies, reduction in the total treatment time has improved tumor control.^[8] A shorter treatment time may be accomplished by applying a higher dose per fraction or by increasing the weekly number of radiation fractions.

The benefit of an increased tumor cell kill because of the large fraction size in a short overall treatment time is counteracted from the radiobiological point of view, by an increased potential for late side effects. However, late radiation toxicity is often less relevant in patients treated in advanced stage setting.

The primary endpoint of this study is to compare the response pattern in patients with non-metastatic, inoperable, locally advanced head and neck squamous cell carcinoma, who are not fit for concurrent chemoradiation or surgery followed by adjuvant therapy, by three modes of radiation with conventional radiation, "Christie" regimen, and pure accelerated radiation (six fractions per week). Secondly the study was studied as designed to determine the toxicity profiles and the disease-free survival and overall survival.

MATERIALS AND METHODS

Between May 2008 and May 2012, 132 patients with chemotherapy, surgery (other than biopsy from primary and or neck nodes for histology confirmation), and radiation naïve non-metastatic, inoperable, locally advanced squamous cell carcinoma of head and neck, AJCC stages III to IVB with tumor characteristics of T3 and T4 with or without N2-3, M0, with reduced creatinine clearance (<60 ml/min), age more than 50 years, significant co-morbidities like uncontrolled diabetes, cardiac disease, poor performance status (ECOG 3 and 4), or a combination of these and willing to give consent

for participation in trial as per Helsinki's declaration were included in this single institutional, interventional, open label, parallel, multi-arm, prospective, randomized controlled study. They were randomized by "computer-based randomization" into three arms: arms: Arm A (n=44) patients received the "Christie Regimen" dose of 50 Gray (Gy) in 16 fractions, 3.125 Gy per fraction, total treatment time 3 weeks; Arm B (n = 42) patients were entailed to receive 66 Gy in 33 fractions in 6 fractions per week, treatment completed in 5.5 weeks; and Arm C (n=46) patients were entailed to receive 66 Gy in 2 Gy per fractions, in 30 fractions in 6.5 weeks, i.e. in conventional fractionation [Figure 1].

Radiotherapy

Prior to radiation all patients were evaluated for baseline pretreatment parameters. The preradiation dental evaluation was completed at least 2-3 weeks prior to treatment. Patients were immobilized in a supine treatment position in a custom-made head-and-neck mask manufactured in the mould room. All patients underwent simulation, using conventional planning. Cobalt 60 machine with average energy of 1.25 MeV was used to deliver the radiation. Two lateral fields were mostly used to treat the primary tumor and/or upper neck with a matched anterior field, as needed for the supraclavicular region.

Response assessment

The primary end point of the study was the response rate (complete response (CR), partial response (PR), and overall response rate (ORR = CR+PR)) (assessment was done by RECIST criteria). The secondary end points were disease-free survival (DFS) and acute (within 90 days of radiation) and late toxicity (beyond 90 days after radiation) (graded according to the RTOG/EORTC Acute and Chronic Radiation Morbidity Scoring) and Overall survival at the end of 4 years of the study.

Patients were evaluated 6-8 weeks after completion of treatment by the ENT surgeon and radiation oncologist. All patients underwent CECT Scan of head and neck along with detailed ENT examination with a directed biopsy performed in patients with clinical and/or radiological suspicion of persistent primary and/or nodal disease. Wherever feasible, patients with residual disease were sent for salvage chemotherapy with combination of taxanes, platinum, and 5-fluorouracil. Salvages surgery for the removal of primary and/or nodal disease was not possible due to co-morbid conditions. After initial assessment, the patients with no evidence of residual primary and nodal disease were evaluated every 3 months till the end of the study to assess the toxicity and the disease-free survival rates.

Nutritional status was maintained with all patients encouraged to liberal oral food intake and in the case of difficulty, the feeding tube was inserted either through

the nasal route, percutaneously, or endoscopically. For patients with respiratory distress, it was sometimes elected to perform tracheostomy before starting radiation.

Statistical analysis

Categorical variables were summarized as frequency and

percentages, and for continuous data mean ± SE with range were calculated. All statistical tests were done using ANOVA and statistical significance was accepted for a calculated P value < 0.05. Disease-free survival (DFS) is defined as the time span from the date of completion of treatment until the date of first recurrence, locoregional or

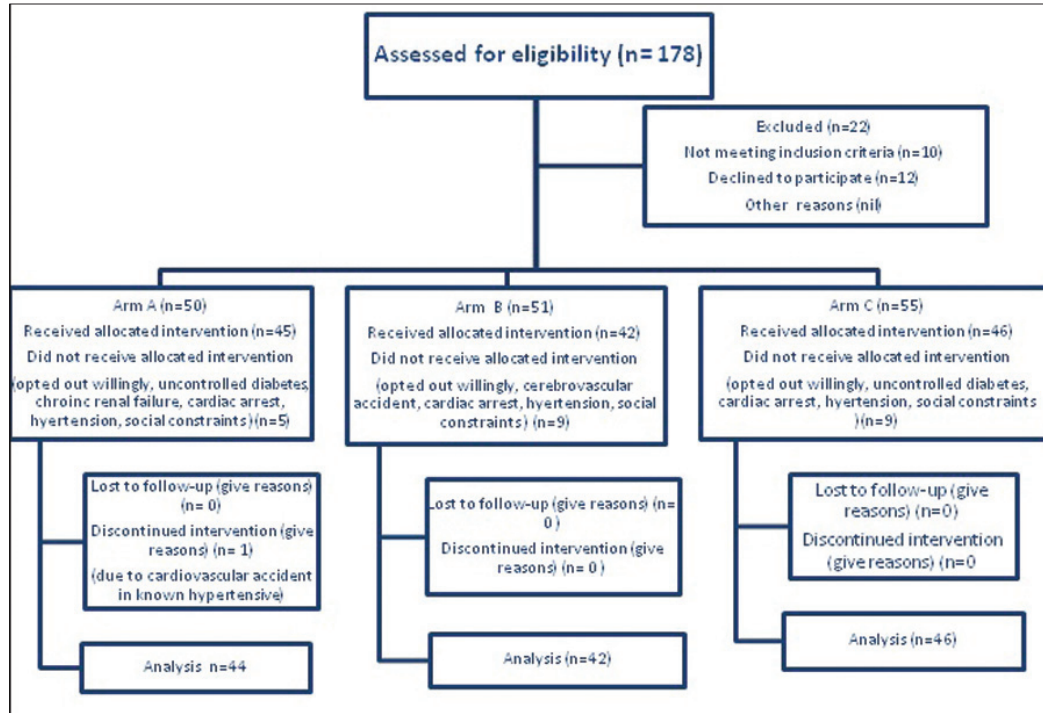


Figure 1: The treatment protocol based on CONSORT proforma

Table 1: Baseline comparison among 3 arms							
Baseline parameters	Groups						P value
	Group A (n=44)		Group B (n=42)		Group C (n=46)		
Age (in years)							0.678
50-59 years	17	38.6%	17	40.5%	19	41.3%	
60-69 years	24	54.5%	21	50.0%	24	52.2%	
70-79 years	3	6.8%	4	9.5%	3	6.5%	
Mean±SE	61.3±0.8		61.1±0.9		61.0±0.8		
Minimum	50		50		50		
Maximum	72		71		73		
Sex							0.954
Male	39	88.6%	35	83.3%	41	89.1%	
Female	5	11.4%	7	16.7%	5	10.9%	
CrCl (ml/min)							0.545
<40 ml/min	8	18.2%	9	21.4%	12	26.1%	
40-49 ml/min	23	52.3%	21	50.0%	24	52.2%	
50-59 ml/min	13	29.5%	12	28.6%	10	21.7%	
Performance status							0.518
ECOG 3	30	68.2%	33	78.6%	35	76.1%	
ECOG 4	14	31.8%	9	21.4%	11	23.9%	
Primary							0.294
Oral cavity	8	18.2%	7	16.7%	12	26.1%	
Oropharynx	17	38.6%	20	47.6%	22	47.8%	
Larynx	15	34.1%	12	28.6%	9	19.6%	
Hypopharynx	4	9.1%	3	7.1%	3	6.5%	
Stage							0.730
Stage IV A	18	40.9%	17	40.5%	20	43.5%	
Stage IV B	10	22.7%	9	21.4%	12	26.1%	
Stage III	16	36.4%	16	38.1%	14	30.4%	

systemic. All other events were censored. The patients who reached a complete response at the end of treatment were considered for disease-free survival time interval. Overall survival and disease-free survival rates were calculated using Kaplan–Meier analysis, SPSS version 17.

RESULTS

87.1% of patients were male with median age 62 years (range: 50-73 years), with the baseline profiles in all the arms comparable [Table 1]. 44.6% had oropharyngeal cancer and 41.6% stage IV A disease. The accrual was completed within 11 months. With a median follow-up of 11 months, the overall treatment time was 21 days for Arm A patients (21-25 days), 39 days for Arm B (38-45 days) and 46 days for Arm C (43-52 days). The overall response rates (CR + PR) were comparable in all arms with 75%, 80%, and 76.1% for arms A, B, and C, respectively (*P* value 0.401) [Table 2]. Stage-wise response rates were high in stage III patients [Table 3]. Of all primaries, the hypopharyngeal cancer patients had the worst response rates with progressive disease in 25-33% of patients and laryngeal cancer patients having best response rates (*P* value = 0.022) [Table 4]. Majority of disease recurrence was at the primary sites. The disease-free survival were in favor of altered radiation and with the log rank test (*P* value 0.034) the mean survival

was 18.103 months (SE 1.017, 95% CI 16.110, 20.096) for arm A (Christie Regimen), 17.526 months (SE 0.804, 95% CI 15.950, 19.102) for arm B (pure accelerated regimen), and for arm C (conventional radiation) 14.289 (SE 1.547, 95% CI 11.256, 17.321) [Figure 2].

Acute grade 3 cutaneous toxicity was reported in 34.1% in arm A in comparison to 28.6% in arm B and 15.2% in Arm C (*P* value 0.018). Mucositis was also high in arms A and B (*P* value 0.011) [Table 5]. Two patients in arm A and 1 in arm B had grade 4 mucositis for which they were hospitalized for conservative management. Despite the high rate of acute skin and mucosal toxicities, there were no dropouts or treatment breaks more than 7 days due to adequate nutritional and supportive management provided to the patients. The chronic grade 2 and 3 toxicities were higher in altered fractionation arms for skin, mucous membrane, and parotid. The overall survival however was not statistically different among the three arms at the end of study period, log rank test chi square 5.349, df 2, *P* value = 0.069 [Table 6 and Figure 3].

Table 2: The Response rate at the end of treatment

Response assessment using RECIST	Groups					
	Group A		Group B		Group C	
Complete response (CR)	18	40.9%	22	52.4%	18	39.1%
Partial response (PR)	15	34.1%	12	28.6%	17	37.0%
Stable disease (SD)	7	15.9%	6	14.3%	5	10.9%
Progressive disease (PD)	4	9.1%	2	4.8%	6	13.0%

Table 3: Stage wise response assessment using RECIST criteria at the end of the treatment.

Stage	Response using RECIST	Groups					
		Group A (n=44) (%)		Group B (n=42) (%)		Group C (n=46) (%)	
Stage III	CR	12	75.0	12	75.0	10	71.4
	PR	2	12.5	3	18.8	1	7.1
	SD	0	0.0	1	6.3	1	7.1
	PD	2	12.5	0	0.0	2	14.3
Stage IV A	CR	5	27.8	8	47.1	6	30.0
	PR	8	44.4	5	29.4	10	50.0
	SD	5	27.8	2	11.8	3	15.0
	PD	0	0.0	2	11.8	1	5.0
Stage IV B	CR	1	10.0	2	22.2	2	16.7
	PR	5	50.0	4	44.4	6	50.0
	SD	2	20.0	3	33.3	1	8.3
	PD	2	20.0	0	0.0	3	25.0

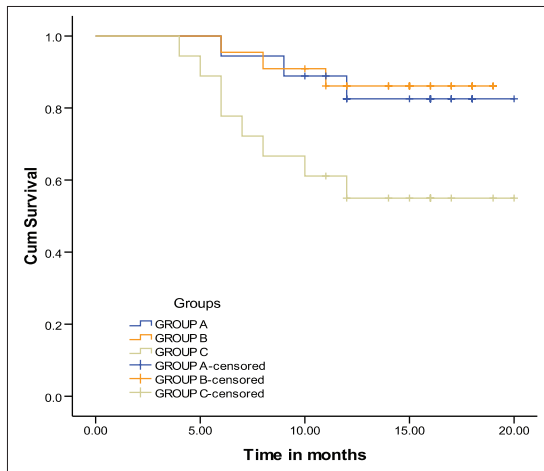


Figure 2: Disease free survival

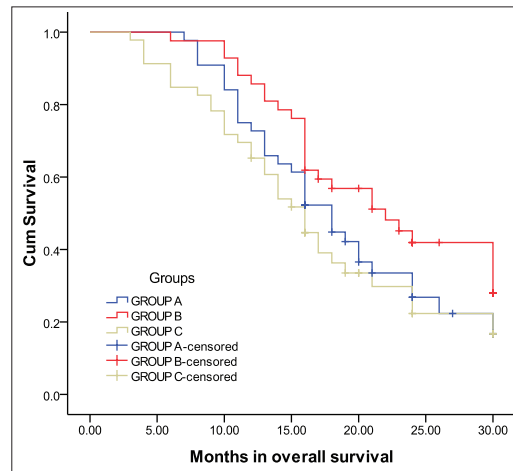


Figure 3: Overall survival at the end of study, log rank test - Chi square test 5.349, df 2, *P* value 0.069

Table 4: Primary site wise response assessment

Primary sites	Response	Groups						P value
		Group A (n=44) (%)		Group B (n=42) (%)		Group C (n=46) (%)		
Oral cavity	CR	4	50.0	6	85.7	4	33.3	0.108
	PR	3	37.5	1	14.3	8	66.7	
	SD	1	12.5	0	0.0	0	0.0	
	PD	0	0.0	0	0.0	0	0.0	
Oropharynx	CR	5	29.4	10	50.0	7	31.8	0.193
	PR	7	41.2	8	40.0	5	22.7	
	SD	4	23.5	1	5.0	5	22.7	
	PD	1	5.9	1	5.0	5	22.7	
Larynx	CR	9	60.0	4	33.3	7	77.8	0.022*
	PR	4	26.7	3	25.0	2	22.2	
	SD	0	0.0	5	41.7	0	0.0	
	PD	2	13.3	0	0.0	0	0.0	
Hypopharynx	CR	0	0.0	2	66.7	0	0.0	0.125
	PR	1	25.0	0	0.0	2	66.7	
	SD	2	50.0	0	0.0	0	0.0	
	PD	1	25.0	1	33.3	1	33.3	

Table 5: Comparison of toxicities

Parameters	Grading	Groups						P value
		Group A (n=44) (%)		Group B (n=42) (%)		Group C (n=46) (%)		
RTOG acute skin toxicity	Grade 0	7	15.9	6	14.3	9	19.6	0.018*
	Grade 1	7	15.9	6	14.3	20	43.5	
	Grade 2	15	34.1	18	42.9	10	21.7	
	Grade 3	15	34.1	12	28.6	7	15.2	
RTOG acute mucositis	Grade 0	7	15.9	5	11.9	9	19.6	0.011*
	Grade 1	7	15.9	7	16.7	20	43.5	
	Grade 2	16	36.4	17	40.5	10	21.7	
	Grade 3	12	27.3	12	28.6	7	15.2	
RTOG chronic (late) skin	Grade 4	2	4.5	1	2.4	0	0.0	0.001*
	Grade 0	12	27.3	13	31.0	25	54.3	
	Grade 1	12	27.3	14	33.3	16	34.8	
	Grade 2	14	31.8	12	28.6	5	10.9	
RTOG chronic (late) mucous membrane	Grade 3	6	13.6	3	7.1	0	0.0	0.001*
	Grade 0	10	22.7	13	31.0	25	54.3	
	Grade 1	14	31.8	14	33.3	16	34.8	
	Grade 2	14	31.8	12	28.6	5	10.9	
RTOG chronic (late) parotid	Grade 3	6	13.6	3	7.1	0	0.0	0.005*
	Grade 0	7	15.9	13	31.0	22	47.8	
	Grade 1	14	31.8	14	33.3	18	39.1	
	Grade 2	17	38.6	12	28.6	5	10.9	
	Grade 3	6	13.6	3	7.1	1	2.2	

RTOG: Radiation therapy oncology group acute and late radiation morbidity scoring

Table 6: Means and medians for overall survival time

Groups	Mean				Median			
	Estimate	Std. error	95% confidence interval		Estimate	Std. error	95% confidence interval	
			Lower bound	Upper bound			Lower bound	Upper bound
Group A	18.738	1.210	16.367	21.109	18.000	1.375	15.305	20.695
Group B	21.807	1.247	19.362	24.251	22.000	3.211	15.706	28.294
Group C	16.942	1.358	14.280	19.605	16.000	1.391	13.273	18.727
Overall	19.110	0.750	17.640	20.581	18.000	0.944	16.150	19.850

DISCUSSION

Over 500,000 patients are diagnosed each year as having cancer of the head and neck, and this account for about 2% of all cancer registrations. It occurs predominantly in an older population, occurring in males more than in females

at all sites. The most common histological type is that of squamous cell carcinoma and is associated with tobacco and tobacco products; 70 - 80% of all cancers in the oral cavity, oropharynx, and larynx in India may be due to smoking or chewing tobacco. Squamous cell carcinoma of the head and neck is predominantly a locoregional disease, and the

primary treatment methods are surgery and radiotherapy.^[1] Head and neck cancer can be cured by radiation with or without chemotherapy, but tumors exhibit heterogeneous intrinsic cellular radiosensitivity. Historically, patients with unresectable HNSCC treated by RT alone have LRC rates between 50 and 70%^[9-11] and 5-year survival rates of 10 - 20%. Most of these patients die of locoregional disease progression.

Radiation therapy with concurrent chemotherapy is superior to single modality fractionation radiotherapy in the nonsurgical management of head and neck cancer. RTOG 81-17 used concurrent chemoradiotherapy (cisplatin based) to treat 134 patients who had unresectable carcinomas of the head and neck.^[12] The response and survival rates favored concurrent cisplatin-based chemoradiation. Multimodality therapy is now a well-established strategy for control of tumors. Other RTOG trials have suggested an increase in the local control for patients treated by concurrent chemoradiotherapy as compared to radiotherapy alone.

However, with presence of co-morbidities, poor performance status, and poor renal function concurrent chemoradiation could not be given to many patients. The important contributing factors include trismus, poor nutritional intake, locally advanced disease often with ulcerated neck nodes, advanced age to mention some. An alternative to chemoradiation is altered fractionated RT. Indeed, a considerable interest has been focused in the last decades on the possibilities of improving the efficacy of radiotherapy when using altered fractionated radiotherapy.

In general, “conventional radiotherapy” involves the delivery of fractionated radiation (commonly 2 Gy daily to 66-70 Gy) and is complicated by the close proximity of tumor and normal tissue structures such as the spinal cord, brain stem, parotid glands, and optic pathway structures. With conventional head and neck radiotherapy, masking techniques, and routine laser alignment, daily set-up variations of 3–6 mm are common. To allow for these variations, and for uncertainties in tumor definition,

generous safety margins are used. While this approach helps to ensure irradiation of all malignant tissue, it also subjects healthy tissue to full dose radiation exposure and the recognized side effects of treatment.

Altered fractionation may involve acceleration, hyperfractionation, or hypofractionation. Radiobiologically the altered fractionation can be compared with conventional fractionated radiation on the basis of BED (biological equivalent dose), the toxicities, and outcomes [Table 7].

The biological effective dose (BED) of radiation can be calculated mathematically:^[13,14]

where D = total dose and d = dose per fraction. The α/β ratio varies from tissue to tissue with late responding tissues having an α/β ratio of 1-3 and acute responding tissues and tumors having an α/β ratio of 8-10.

Attempts to improve on both the efficacy and toxicity profile for head and neck radiotherapy led to the development of a number of alternative delivery schedules, employing different fractionation regimens.^[9,15]

Accelerated hyperfractionation is a strategy intended to improve the likelihood of cancer control by delivery of a higher total dose of radiation without an offsetting increase in severe late normal tissue complications. The early results of a recently completed randomized trial of a 4-week hyperfractionated radiation schedule, and of two other regimens of accelerated hyperfractionation, confirm to some degree the biological hypotheses on which this strategy is based.^[16]

Accelerated fractionation involves a reduction in the overall treatment time, with (hybrid) or without (pure) change in fraction size and total dose. Acceleration is based on the fact that the reduced overall treatment time reduces the opportunity for tumor cell regeneration. The reduction in overall treatment time, however, can influence the response of healthy tissue and will lead to an increase in

Table 7: Rationality of altered radiation fractionation

Types of fractionation	Characteristics	Rationale	Results
Hyperfractionation	Total dose: Same Dose per fraction: Reduced Number of fractions: Increased Overall time: Same	Reduce dose per fraction reduces late effects Higher total dose increase tumor kill	Local control: Better Acute toxicity: Higher Late toxicity: Less
Accelerated fractionation	Total dose: Reduced Dose per fraction: Reduced/same Number of fractions: Same Overall time: Reduced	Reduced time reduces tumor repopulation Reduce dose per fraction reduces late effects	Local control: Better Acute toxicity: Higher Late toxicity: Less
Hypofractionation	Total dose: Reduced Dose per fraction: Increased Number of fractions: Reduced Overall time: Reduced	Reduced time Repopulation reduced	Local control: Less Acute toxicity: Less Late toxicity: Higher

acute side effects. Altered fractionation has also shown potential efficacy in the post-operative setting for head and neck cancer. In one study, compared with conventional fractionation (60 Gy over 6 weeks, 2 Gy per fraction, treating 5 days per week), the use of accelerated hyperfractionation (46.2 Gy per 33 fractions (1.4 Gy per fraction) over 12 days, treating 6 days a week) led to a significantly improved 3 year locoregional control rate (88% vs. 57%, $P=0.01$).^[17] However, acute toxicity is enhanced and there was no significant difference in the overall survival between the groups.

The EORTC (split course) accelerated protocol^[5] introduced a deliberate break in treatment to allow 72 Gy to be delivered in 45 fractions over a total of 5 weeks. This regimen produced a 13% improvement in locoregional control over the conventional arm (70 Gy in 35 fractions over 7 weeks), but both acute and late morbidities were increased substantially. It was speculated that the observed increase in late effects may have been due to insufficient intervals (4 h) between fractions. However, it is also possible that the increase in acute toxicity resulted in consequential late radiation injury.

The importance of even small amounts of acceleration was emphasized by the results from the Danish Head and Neck Cancer Study Group (DAHANCA) 6 and 7 trial.^[6] A 1 week reduction in overall treatment time by giving six fractions per week instead of five fractions per week achieved a 10% improvement in locoregional control with no impact on late morbidity. It did result in increased confluent mucositis (66% versus 46%), but the skin toxicity was the same.

The Continuous Hyperfractionated Accelerated Radiotherapy Trial (CHART)^[18] showed that acceleration can produce equivalent results to conventional radiation even when significant reductions in overall dose occur. In this study, 54 Gy in 36 fractions over 12 days was compared with a conventional arm of 66 Gy in 33 fractions over six-and-a-half weeks. There was no improvement in locoregional control compared to the conventional arm, with the exception of advanced laryngeal tumors. Acute morbidity was increased in CHART but the reduction in total dose and dose per fraction was associated with a reduction in later morbidities including osteochondritis, skin telangiectasia, mucosal ulceration, and laryngeal edema.

A meta-analysis of accelerated protocols has been performed.^[19] There were eight randomized trials without dose reduction and five with a total dose reduction. The hazard ratio for death for the first group was 0.97 (0.89 - 1.05) and for the second group was 0.92 (0.86 - 0.97). The absolute survival improvement at 5 years was 2% and 1.7%, respectively, and the improvements in locoregional control at 5 years were 7.3% and 2.3%.

The patients deemed inoperable and not fit to withstand the burden of CRT still require some form of treatment even if it is with palliative intent to control their locoregional disease and to alleviate their disturbing symptoms. Although the information about the optimal hypofractionated palliative regimen for incurable HNSCC in the current literature is scanty, an optimal palliative RT schedule is one that would provide worthwhile regression of the tumor and local symptoms within a short OTT with minimal toxicity. First, the treatment is completed before accelerated repopulation becomes a significant radiobiological factor. Second, the reduction in the number of fractions also allows a more efficient use of resources, which can help avoid long waiting times for other patients and lastly, considering that this group of patients are usually of older age and often have a poor performance status as well as significant co-morbidities, it is almost mandatory to keep the OTT as short as possible. From radiobiological, economic, and logistical points of view, a hypofractionated schedule would be the most suitable option.

Hypofractionated radiotherapy utilizes a small number of fractions with a larger dose per fraction. The overall time is usually shorter than an accelerated protocol. These regimes produce worse late effects than conventional fractionation when used in the curative setting.^[20] The acute reactions are acceptable if treatment volumes are kept small and tolerability can be improved by introducing treatment breaks into the protocol.

This type of schedule is most suited to the patient with poor performance status in whom the aim of treatment is to palliate symptoms and cause as little as possible in the ways of side-effects. These patients have a poor prognosis with a median survival of 4-8 months.^[21]

There are a number of phase I and II studies that have looked at hypofractionated palliative radiotherapy for advanced SCC of the head and neck. The QUAD SHOT^[22] was developed with the aim of delivering short intense doses of radiation that were below the threshold for mucositis. The protocol consists of 14 Gy in four fractions over 2 days and can be repeated in responders up to a total dose of 42 Gy in 12 fractions. In patients with very advanced disease and poor performance status, objective responses were produced in 53% of cases and 44% had improvements in their quality of life. Other palliative schedules include that of Paris,^[23] who used 3.7 Gy twice a day for 2 days and repeated this monthly for 3 months. Although 40% did not complete the full course, responses were achieved in 77% of cases. The hypofractionated schedule involved treating patients twice per week in 6 Gy fractions to a total dose of 30-36 Gy. This is well tolerated in terms of acute reactions and is equivalent to 40 Gy in 2 Gy fractions in terms of tumor

and mucosal effects. Comparing these protocols with each other is difficult because of the heterogeneity of advanced SCC of the head and neck and the problems associated with measuring quality of life rather than just survival.

The Christie Hospital in Manchester developed a 3-week schedule of RT during World War II when RT facilities were limited. Results were found not to be different from the conventional schedules used in the previous treatment periods in terms of local control and toxicity.^[24,25] This schedule was, therefore, adopted by Christie hospital and number of other British cancer centers as a standard RT schedule for early-stage laryngeal cancer. Many randomized and non-controlled trials have also shown no difference in local control between conventional and hypofractionated schedules.^[26] Surprisingly, many of these schedules gave less severe late normal tissue reaction than expected given the short OTT and the high fraction dose.^[26-30]

In the clinical study "Three weeks radiotherapy for T1 glottic cancer: the Christie and Royal Marsden Hospital Experience," 200 patients (100 from each center) with T1 glottic invasive squamous cell carcinoma treated with definitive radiotherapy between 1989 and 1997 were analyzed. The median age was 68 years. All patients received once daily fractionation, 5 days a week to a total tumor dose of 50.0–52.5 Gy in 16 fractions; the fraction size ranged from 3.12 to 3.28 Gy. The median follow-up period was 5 years and 10 months.^[7] The patients were treated with a continuous course of radiotherapy using megavoltage photons. The treatment time was 21 days in 69% of cases, with a range of 21–26 days. The Christie Hospital patients were all treated with 4-MV photons; the Royal Marsden patients were treated with either 5- or 6-MV photons. The dose specified at the ICRU reference point was 52.5 Gy at the Christie Hospital and 50 Gy at the Royal Marsden; the fraction sizes were 3.28 and 3.12 Gy, respectively.

Erasmus MC-Daniel den Hoed Cancer Center adopted for a cohort of palliative patients a hypofractionated radiation schedule, comparable to that used in the Christie hospital. The purpose of this study is twofold. First, to evaluate the response rates, toxicity, and survival in the patients treated and the impact of this schedule on the quality of life (QoL) in patients surviving 1 year after completion of treatment. 74% of patients were male, 31% had oropharyngeal cancer, and 81% stage IV disease. With 45% complete response and 28% partial response, an overall response rate of 73% was achieved, 6% had stable disease, and 21% progressed during or directly after completion of treatment. The median survival time was 17 months and 62 patients (40%) survived 1 year after RT. The actuarial rates of locoregional control, disease-free survival, and overall survival were 62%, 32%, and 40% at 1 year and 32%, 14%, and 17% at 3 years. Acute grade 3 skin and mucosal toxicities were observed in 45%

and 65% of patients, respectively. Severe late toxicity was reported in 4.5% of patients. Of patients surviving 1 year after RT, a retrospective chart review showed that 50% gained weight, pain improved in 77%, performance status in 47%, and only 29% of them was still feeding-tube dependent.

The Christie Hospital in another randomized trial for locally advanced head and neck cancer treated patients with hypofractionated radiation (50 - 55 Gy in 15 or 16 fractions) with concurrent single agent methotrexate (MTX) 100 mg/m² given at the commencement of and after 2 weeks of a 3-week course of treatment. Mucositis was significantly greater in the patients receiving MTX, but there was no difference in long-term toxicity. The addition of MTX increased local control from 50% to 70% ($P = 0.02$) and survival from 37% to 47% ($P = 0.07$). The greatest benefit was seen in patients with oropharyngeal primaries who constituted one-third of the study population.^[31]

Our results were similar to the findings in the study of Levendag *et al.*^[10] and Schofield *et al.*^[25] who suggested that LRC and DFS rates are better in tumors of the oropharynx and larynx, compared to those of oral cavity and hypopharynx. The benefit of increased locoregional control of accelerated regimen as noted in the study is comparable with the results of the DAHANCA 6 and 7 clinical trials and Awaad *et al.*^[6,17] When comparing hypofractionated "Christie regimen" with standard conventional radiation protocol, our results were similar with the results of the clinical study at Erasmus MC-Daniel den Hoed Cancer Center, with ORR 75% versus 73%.

CONCLUSION

Hence, it can be concluded that although there was no difference in ORR, DFS was in favour of altered fractionation schedules with manageable toxicities in altered fractionation. The total time needed were less in accelerated and hypofractionated radiotherapy regimens, and this radiobiological superiority is beneficial for centers like ours where the patient load is much higher than the facility available for radiation. Further studies with longer follow-up will be needed for confirmation to establish the long-term effects of altered radiation over conventional one.

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