Original Article

Hypofractionated versus conventional radiotherapy with or without chemotherapy in head and neck cancer: A comparative study

Somnath Roy, Chandrani Mallik, Suman Ghorai, Avijit Hazra[1], Anup Majumdar

Departments of Radiotherapy and [1]Pharmacology, Institute of Post Graduate Medical Education and Research and SSKM Hospital, Kolkata, West Bengal, India

ABSTRACT

Background: To investigate tumor response and toxicities in head and neck squamous cell cancer (HNSCC) upon hypofractionated radiotherapy compared with conventional fractionation. **Settings and Design:** Data from patients with squamous cell cancer of oral cavity, oropharynx, hypopharynx, and larynx (AJCC, 2010 Stage II to IVB); who received hypofractionated ($n = 30$) or conventionally fractionated ($n = 30$) radiotherapy, with or without chemotherapy, between January 2010 to June 2011 were retrieved and retrospectively analyzed. **Materials and Methods:** In conventional arm (Arm A), each patient received 70 Gy at 2 Gy per fraction over 7 weeks, along with concurrent cisplatin (100 mg/m^2) on days 1, 22, and 43 for locally advanced stage. In hypofractionated arm (Arm B), each patient received 55 Gy at 2.75 Gy per fraction over 4 weeks, along with concurrent cisplatin (100 mg/m^2) on days 1 and 22 for locally advanced stage. The end points were tumor response, acute and late toxicities, overall survival (OS), and diseases-free survival (DFS). **Results:** The tumor response distribution was comparable – 24 (80%) patients in arm A and 23 (76%) in arm B achieved a complete response. Significant differences in frequencies of acute grade ≥ 2 skin toxicity, mucositis were found, with higher frequencies in Arm B. Higher frequencies of late grade ≥ 2 dysphagia, laryngeal edema, xerostomia, and confluent mucositis were encountered in Arm B at 6 months from start of chemoradiation. However, OS, DFS, and loco-regional recurrence rates were comparable between the two arms. **Conclusions:** Hypofractionated radiotherapy can achieve similar tumor response to conventionally fractionated radiotherapy in HNSCC, although with some increase of toxicity.

Key words: Chemoradiation, conventional fractionation, head neck cancer, hypofractionation

INTRODUCTION

Squamous cell carcinoma of head and neck (HNSCC) is being increasingly treated by multimodality approaches combining surgery, radiotherapy, and chemotherapy. Randomized controlled trials have demonstrated major improvements in loco-regional tumor control from altered fractionation radiotherapy with or without chemotherapy as compared with conventional fractionation. Altered fractionation schedules seek to improve the therapeutic ratio between tumor cell kill and normal tissue damage by exploiting the dissociation between acute and late radiation effects. Hypofractionated radiotherapy utilizes a small number of fractions with a larger dose per fraction, shortening overall treatment time compared to a conventional protocol. Although a shorter treatment time can be obtained by applying a higher dose per fraction, it might also result in a disproportionate increase in the incidence of late complications.

In the United Kingdom, an audit has shown that although most centers adopt conventional 2 Gy fractionation, a substantial proportion of patients receive a hypofractionated prescription with larger doses per fraction, such as 55 Gy in 20 fractions (2.75 Gy/fraction).[1,2] This regimen has the theoretical advantage that the treatment is completed before accelerated repopulation becomes a significant radiobiologic factor.

The linear quadratic model predicts for similar $\log_{10}$ tumor cell kill at 10.26 and a lower biologically effective dose (BED)

Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.152718

Address for correspondence: Dr. Somnath Roy, Institute of Post Graduate Medical Education and Research and SSKM Hospital, 242 A.J.C. Bose Road, Kolkata - 700 020, West Bengal, India. E-mail: drsomnath1980@gmail.com

to late effect tissues of 105.4 Gy_3 versus 116.6 Gy_3 (assuming Tp [potential doubling time] =3 [0.67 Gy_{10}/d], Tk [the time taken from the start of radiotherapy to commencement of accelerated repopulation] =21); α/β =10 Gy for tumor, α/β =3 Gy for late-responding tissue. In addition, it predicts for tolerable acute mucosal reaction with a BED of 55.9 (assuming Tp = 2.5 [0.8 Gy_{10}/d], Tk = 7 days, $\alpha = 0.35 lnGy^{-1}$, α/β =10 Gy).[3]

The objective of this study was to investigate tumor response in HNSCC using hypofractionated radiotherapy compared with conventional fractionation with or without concurrent chemotherapy.

MATERIALS AND METHODS

Data of 60 patients with biopsy-proven squamous cell cancer of oral cavity, oropharynx, hypopharynx, and larynx (AJCC, 2010 Stage II to IVB), who received either hypofractionated (n = 30) or conventional fractionation (n = 30) radiotherapy, with or without concurrent chemotherapy, between January 2010 to June 2011 were retrieved and retrospectively analyzed. Individual case notes and all treatment related information were obtained from institutional cancer registry. The study protocol was approved by the Institutional Ethics Committee. Sampling was purposive with the recruitment target of 30 subjects per arm.

The information collected included patient age, tumor site, stage, chemotherapy used with regimen details and number of cycles administered, radiation dose administered, overall treatment time, pre- and post-therapy contrast-enhanced computed tomography (CT) scan findings of head and neck, hematological, biochemical and chest X-ray findings, acute and late toxicity data and subsequent salvage therapy. Patients with nasopharyngeal carcinoma, Stage IVC disease, evidence of distant metastasis, previous radiotherapy or concurrent chemoradiation within the intended treatment volume, contraindications to chemotherapy and Eastern Cooperative Oncology Group status ≥ 3 were excluded.

The outcome measures studied were tumor response, acute and late toxicities, disease-free survival (DFS), and overall survival (OS), with emphasis on toxicities as the primary outcome. Response evaluation was done periodically after completion of treatment based on clinical examination and contrast enhanced CT scan of head and neck and chest X-rays findings in each patient. Biopsy or fine-needle aspiration cytology was taken from any suspicious clinical and or radiological residual tumor or to confirm recurrence at primary site and or nodal area. Patients were then categorized as per Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1) as having complete response (CR), partial response (PR), stable disease (SD), and progressive disease. No planned neck dissection was done before or after radiation. In cases of residual tumor, recurrence, or progression of the disease, salvage surgery was done, or palliative chemotherapy given, depending on the status of the individual patient, symptoms, and co-morbidities.

Patients were evaluated for toxicity weekly during radiation and thereafter during follow-up at initially monthly and subsequently at longer intervals. Acute toxicity (within 90 days of the start of therapy) was graded according to the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity criteria. Toxicities appearing after 90 days were regarded as late toxicity and assessed at 6, 12, and 18 months from start of chemoradiation. Late toxicity was scored according to RTOG chronic radiation morbidity criteria and National Cancer Institute Common Terminology Criteria for Adverse Events version 4 where applicable. OS and DFS were estimated from Kaplan–Meier survival plots.

Radiotherapy and chemotherapy protocol

All patients underwent simulation, and treatment was delivered through the megavoltage beam with Cobalt-60 using conventional two-dimensional treatment planning. Two parallel opposed lateral fields were used to treat the upper neck with a matched anterior lower field, as appropriate with proper immobilization in both arms without any tissue compensators. "Off cord" field was practiced for all patients after 45 Gy in conventional fractionation and after 35.75 Gy in hypofractionated arm. In conventional arm (Arm A), the intended radiation dose to the primary tumor and involved nodes was 45 Gy in 23 fractions over 4½ weeks (phase I) followed by up to 51 Gy in 26 fractions over 5½ weeks after sparing of spinal cord (phase II) and final total dose of 70 Gy in 35 fractions over 7 weeks (phase III) was delivered through additionally reduced portals with a margin of 2 cm around the original gross diseases. Similarly in hypofractionated arm (Arm B), 35.75 Gy in 13 fractions over 2½ weeks was given to primary and draining lymph nodes (phase I) followed by up to 41.25 Gy in 15 fractions over 3 weeks after sparing of spinal cord (phase II) and final total dose of 55 Gy in 20 fractions over 4 weeks (phase III) was delivered through additionally reduced portals with a margin of 2 cm around the original gross diseases. In hypofractionation, the BED corrected for time, Gy_{10} is 66.27 Gy_{10} (i.e. tumor Gy_{10} is 70.12 Gy and proliferation correction Gy_{10} is 3.85 Gy and BED corrected for time is 70.12 Gy −3.85 Gy = 66.27 Gy_{10}).

Fifteen patients with loco-regionally advanced disease in conventional arm received three cycles of concurrent cisplatin (100 mg/m^2) intravenous on days 1, 22, and 43; whereas in hypofractionated arm 15 patients with

loco-regionally advanced diseases; two cycles of concurrent cisplatin (100 mg/m^2) intravenous on days 1 and 22 was given with proper premedication and hydration.

Statistical analysis

GraphPad Prism version 5 (San Diego, California: GraphPad Software Inc., 2007) and SPSS version 16 (Illinois, Chicago: SPSS Inc., 2006) software were used for statistical analysis. Categorical variables were expressed as counts and percentages and compared between groups by Pearson's Chi-square test or Fisher's exact test as appropriate. The Chi-square for trend analysis was also used where applicable. Continuous variables were summarized by mean ± standard deviation, when normally distributed, and compared between groups using Student's unpaired *t*-test. The median and interquartile range was calculated for nonparametric data. Survival analysis was performed to generate the Kaplan–Meier plots for OS and DFS. Survival estimates were compared between groups by log-rank test. 95% confidence interval estimates have been provided where deemed relevant. A $P < 0.05$ was considered statistically significant.

RESULTS

A total of 60 patients meeting the study criteria were identified and included in this study. Table 1 lists the baseline demographic and clinical characteristics in the study arms. In hypofractionated arm median treatment time was 33 days (interquartile range 32–35 days), whereas in a conventional arm, median treatment time was 53 days (interquartile range 51–55 days).

Response evaluation was done periodically after completion of treatment and patients were categorized as per RECIST criteria (version 1.1). A total of 47 (78%) patients achieved CR; 24 (80%) in a conventional arm and 23 (76%) in hypofractionated arm. These numbers were statistically comparable.

On subgroup analysis, CR rate for larynx was 86%; (77% in Arm A and 88% in Arm B) followed by oral cavity 85%; (100% in Arm A and 75% in Arm B), oropharynx 78%; (75% in Arm A and 80% in Arm B), and hypopharynx 56%; (60% in Arm A and 50% in Arm B). Three patients (10%) in Arm A and 2 (6.7%) in Arm B achieved PR. Three patients (10%) in Arm B and 1 (3.3%) in Arm A had diseases progression despite therapy and two patients (6.7%) in each arm had SD.

Three patients out of 13 in the non-CR group underwent salvage neck dissection for nodal stage N2b and worse. Five patients out of 13 in this group died due to non-oncological cause, and five patients underwent salvage chemotherapy

Table 1: Baseline demographic and clinical characteristics of the two study arms

Baseline characteristic	Conventional arm *n*=30	Hypofractionated arm *n*=30	*P**
Age (years)			
Range	37-65	30-65	0.50
Mean±SD	55.9±7.50	54.4±9.59	
Sex			
Male: female	24 (80):6 (20)	23 (77):7 (23)	1.00
Site of primary lesion			
Larynx	13 (43)	9 (30)	0.63
Oral cavity	8 (27)	12 (40)	
Oropharynx	4 (13)	5 (17)	
Hypopharynx	5 (17)	4 (13)	
Tumor size			
T1-T2	20 (67)	18 (60)	0.78
T3-T4b	10 (33)	12 (40)	
Nodal status			
N0	19 (63)	19 (63)	0.67
N1	6 (20)	4 (13)	
N2	4 (13)	5 (17)	
N3	1 (3)	2 (7)	
Stage			
II	15 (50)	15 (50)	0.89
III	8 (27)	7 (23)	
IVA	5 (17)	6 (20)	
IVB	2 (7)	2 (7)	

There were no statistically significant differences in baseline parameters. **P* value in last column: is unpaired *t*-test for age; Fisher's exact test for gender and tumor size; Chi-square for primary site and chi-square for trend for stage and nodal status. SD: Standard deviation

Table 2: Response distribution by RECIST

Tumor response category	Conventional arm *n*=30 (%)	Hypofractionated arm *n*=30 (%)
CR	24 (80.0)	23 (76.0)
PR	3 (10.0)	2 (6.7)
SD	2 (6.7)	2 (6.7)
PD	1 (3.3)	3 (10.0)

Values denote count (percentage) within respective group. The chi-square for trend *P* value (0.46) is nonsignificant for this response distribution. CR: Complete response, PR: Partial response, SD: Stable diseases, PD: Progressive diseases, RECIST: Response Evaluation Criteria in Solid Tumors

Table 3: Response evaluation by subgroup analysis

Site	Response by RECIST criteria*	Conventional arm	Hypofractionated arm	*P*
Hypopharynx	CR	3 (60)	2 (50)	0.21
	PR	2 (40)	0 (0)	
	SD	0 (0)	1 (25)	
	PD	0 (0)	1 (25)	
Larynx	CR	10 (77)	8 (88)	0.28
	PR	1 (8)	1 (11)	
	SD	1 (8)	0 (0)	
	PD	1 (8)	0 (0)	
Oral cavity	CR	8 (100)	9 (75)	0.14
	PR	0 (0)	1 (8)	
	PD	0 (0)	2 (17)	
Oropharynx	CR	3 (75)	4 (80)	1.00
	SD	1 (25)	1 (20)	

Values denote count (percentage) within respective group. The *P* value in the last column is from chi-square for trend for the first 3 site's data and fisher's exact test for the oropharynx data. *RECIST: Response Evaluation Criteria in Solid Tumors, CR: Complete response, PR: Partial response, SD: Stable diseases, PD: Progressive diseases

as they were medically unfit for surgery. Tables 2 and 3 depict response pattern in each arm.

The most prevalent acute toxicities were skin, mucosal, dysphagia, and salivary gland related. The acute grade ≥ 2 skin toxicity were significantly higher in Arm B than in Arm A (76.7% vs. 36.7%; P = 0.004). Grade ≥ 2 mucositis was also higher in hypofractionated arm (80% in Arm B vs. 33.3% in Arm A; $P \leq 0.001$). Minimal grade 3 mucositis was experienced by nine patients (30%) while four patients (13%) had grade 4 mucositis in hypofractionated arm.

Combined grades 2 and 3 dysphagia was noticed – 20% in Arm B versus 6.7% in Arm A (P = 0.25). Grade 3 dysphagia was seen in two patients (7%) in hypofractionated arm, for which a feeding tube through the nasal route was used for 4 weeks. Acute combined grades 2 and 3 salivary gland toxicity was 6.7% in Arm B and 16.7% in Arm A (P = 0.42).

The acute toxicity data are presented in Table 4.

Prolonged grade 3 mucositis, defined as present for ≥ 4 weeks, was encountered in 8 (33%) patients in hypofractionated arm. Admission to the hospital was required for 15 patients with treatment delay for a median duration of 7 days (range 2–11). The reasons for admission were as follows: rehydration and nutritional support, vomiting, symptoms control for mucositis, packed cell transfusion, and growth factor supports.

Late toxicities were observed at 6, 12, and 18 months from start of chemoradiation and are summarized in Table 5. Most of the late toxicities of grade 2 or higher severity were observed within the 1st year from the start of chemoradiation, and late toxicity rate declined over time. Notable late toxicities were salivary gland effects, laryngeal edema, persistent dysphagia, and prolonged mucositis.

Grade 2 or worse late salivary gland toxicity (xerostomia) developed in 18 (64%) patients in Arm B and 4 (15%) patients in Arm A (P = 0.005) at 6 months from start of chemoradiation. Statistically significant differences were also encountered in the frequencies of grades 2 dysphagia and laryngeal edema (14% vs. 4% [P = 0.01] and 25% vs. 15% [P = 0.02] in Arm B and Arm A, respectively) at 6 months from start of chemoradiation. Grade 2 or worse prolonged confluent mucositis was seen in 79% in Arm B versus 15% in Arm A (P = 0.001) at 6 months from start of chemoradiation.

The median follow-up period in this study was 17 months (range 2–28 months; interquartile range 12–23.5 months). Figure 1 depicts Kaplan–Meier estimate of OS. This was comparable between groups – median OS was 16 months (range 4–28 months; interquartile range 9–23 months) in conventional arm versus 17 months (range 2–28 months; interquartile range 13–25 months) in hypofractionated arm.

Figure 2 depicts Kaplan–Meier estimate of DFS. This was also comparable between groups – median DFS was 11 months (range 5–25 months; interquartile range 6–18 months) in conventional arm versus 13.5 months (range 1–18 months; interquartile range 9–22 months) in hypofractionated arm.

There was also no significant difference in terms of diseases recurrence – 8 (26.7%) patients in a conventional arm and 5 (16.7%) in hypofractionated arm had local or regional diseases recurrence.

DISCUSSION

Our study shows that hypofractionated radiotherapy given to patients with HNSCC, results in similar loco-regional control (LRC) compared to conventionally fractionated schedule. The addition of concurrent chemotherapy in locally advanced stage with this hypofractionated regimen, therefore, offers an attractive method to improve tumor control probability and maximize service productivity.

In the meta-analysis of radiotherapy in carcinomas of the head and neck (MARCH), encompassing 15 phase III trials and 6,515 patients, there was 3.4% OS benefit at 5 years for altered fractionation versus conventional fractionation, with most benefit suggested for hyperfractionation.[4] Concomitant chemotherapy with standard fractionation has repeatedly been shown to offer improved LRC and survival. Both altered fractionation and chemoradiotherapy have been shown to be better than conventional treatment

Table 4: Frequency of acute treatment-related toxicities in the two study arms

Acute toxicity	Toxicity grade 2 and above (%)		Toxicity grade 0 and 1 (%)		*P*
	Conventional	Hypofractionated	Conventional	Hypofractionated	
Acute skin	11 (36.7)	23 (76.7)	19 (63.3)	7 (23.3)	0.004
Mucositis	10 (33.3)	24 (80.0)	20 (66.7)	6 (20.0)	<0.001
Dysphagia	2 (6.7)	6 (20.0)	28 (93.3)	24 (80.0)	0.25
Xerostomia	5 (16.7)	2 (6.7)	25 (83.3)	28 (93.3)	0.42

Values denote count (percentage) within respective group. The *P* value in the last column is from fisher's exact test

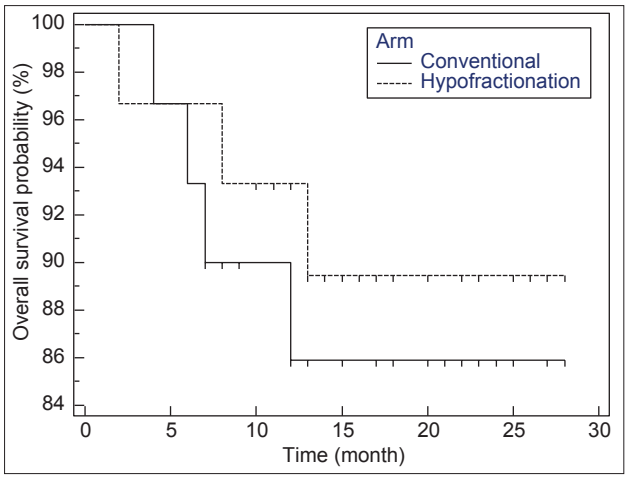

Figure 1: Kaplan–Meier plot showing overall survival probability in two study arms. (Log-rank test *P* = 0.63; hazard ratio for conventional arm vs. hypofractionated arm 0.699 [95% confidence interval 0.159–3.076])

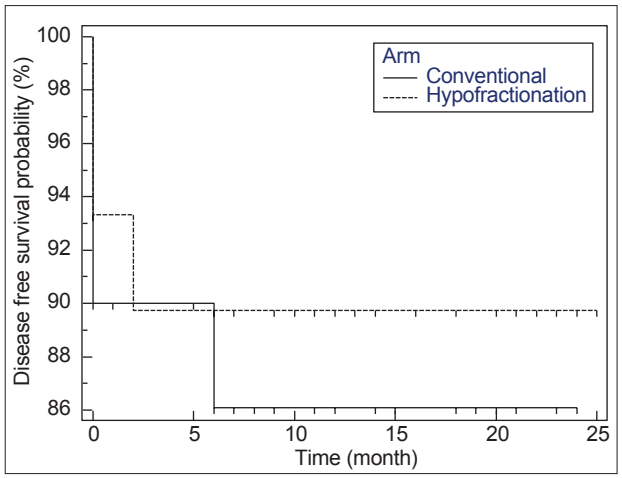

Figure 2: Kaplan–Meier plot showing disease-free survival probability in two study arms. (Log-rank test *P* = 0.67; hazard ratio for conventional arm vs. hypofractionated arm 0.733 [95% confidence interval 0.167–3.224])

Table 5: Frequency of late treatment-related toxicities in the two study arms

	Grade								
	6 months (*n*=55)			12 months (*n*=46)			18 months (*n*=27)		
	2	3	4	2	3	4	2	3	4
Conventional									
Mucosa(%)	11	4	0	5	0	0	0	0	0
Salivary(%)	11	4	0	5	0	0	9	0	0
Dysphagia(%)	4	0	0	0	5	0	0	0	0
Larynx(%)	15	0	0	19	0	0	0	0	0
Hypofractionated									
Mucosa(%)	29	32	18	44	24	8	25	6	0
Salivary(%)	32	25	7	40	12	0	31	0	0
Dysphagia(%)	14	0	0	8	4	0	0	0	0
Larynx(%)	29	0	0	12	0	0	6	0	0

Values denote percentage within respective group

schedules, and meta-analyses indicate that they confer about the same level of benefit in terms of LRC and survival.[4-6]

Sanghera *et al*. analyzed 81 patients with squamous cell cancer of the larynx, oropharynx, oral cavity, and hypopharynx (International Union against Cancer Stages II-IV), who received hypofractionated radiotherapy with dose of 55 Gy in 20 fractions with concurrent chemotherapy. The 2-year local control rate was 75.4%. The 2-year OS rate was 71.6%, and the 2-year DFS rate was 68.6%.[7]

A multi-institutional trial of hypofractionated intensity-modulated radiation therapy for early stage oropharyngeal cancer showed that moderately hypofractionated radiotherapy without chemotherapy for early oropharyngeal cancer is feasible, achieving high tumor control rates and reduced the salivary toxicity.[8] Another prospective trial done by Bakst *et al*. in carcinoma nasopharynx, using 2.34 Gy per fraction for a total of 70.2 Gy did not result in increased acute toxicities of the skin, mucous membranes, or salivary glands indicating that treatment was well-tolerated. Furthermore, no patients required significant treatment breaks nor did any patient require their chemotherapy to be withheld during radiation.[9] Phase I dose escalation trial without concurrent chemotherapy indicated that 2.36 Gy per fraction for a total of 70.8 Gy was the maximal tolerable dose delivered to the gross tumor volume while using a simultaneous integrated boost for head and neck cancers.[10]

With a median follow-up of 17 months, the LRC rate was nearly similar for hypofractionated group in comparison with a conventional group (76% vs. 80%). When analyzed by subgroup [Table 3], the benefit of hypofractionation was probably more pronounced in patients with tumors of the oral cavity and oropharyngeal cancer; however, the differences in primary site distribution was comparable in our study.

To speed up irradiation time by hypofractionation is a relevant alternative to conventional regimens with concerns about the late toxicities produced by this treatment modality. Therefore, although there is no doubt that hypofractionation offers major potential advantages to patients and to the economy of health systems, their development should not be at the expense of a lower likelihood of tumor control as well as of an unacceptable late toxicity.[11-14]

Di Nicola *et al*. analyzed the voice quality and local control in patients with cT1a squamous cell carcinoma of true vocal cords treated with conventional or hypofractionated radiotherapy, and showed that overall voice quality returned to normal levels in 75% of patients 12 months after radiotherapy while modest modifications were observed in 25% of patients. After 3 years of follow-up, the LRC rate was 100% for the patients treated with > 2 Gy/fraction and 96% for the patients treated with 2 Gy/fraction.[15] In addition,

both regimes of radiation therapy achieve similar results in terms of local control and complications.[15,16]

To counteract tumor hypoxia, the addition of a hypoxic cell radiosensitizer at high doses per fraction is shown to be a potential strategy to obtain similar or greater levels of cell killing than achieved with conventional fractionation.[17] Wouters and Brown have previously shown that cells at intermediate oxygen levels are responsible for determining tumor response in conventionally fractionated radiotherapy.[18] However, decrease in cell killing with increasing dose per fraction is attributed to changes in the effective radiosensitivity (alpha/beta) of tumors with heterogeneous oxygenation, a reduction in interfraction reoxygenation and an increased importance of maximally resistant cells (i.e. the hypoxic fraction) in determining overall dose response as the total dose is delivered in fewer fractions.[19-21] However, as the treatment is completed before the tumor cells enter into the phase of accelerated repopulation, this may result in better cell killing and decreased chance of resistance.

Acute morbidity such as mucositis, dermatitis, and dysphagia tended to persist longer in patients who underwent hypofractionated treatment [Table 4]. Fortunately, most patients had manageable acute toxicities.

The presentation of standardized late toxicity data in published reports remains limited. Comparisons of such toxicity data are hampered by a variety of different grading systems and the subjective nature of some assessments.[22] Detailed late toxicity was given for a small number of late surviving patients in the final report of the 94–01 trial performed by the Groupe d'Oncologie Radiotherapie Tete Et Cou.[23] With a median follow-up of 5.5 years for the living patients, they reported the rate of late grade 3/4 toxicity to be as high as 56% in the combined chemoradiation arm.

In a report by Staar *et al*., 30% of patients surviving > 2 years remained dependent on a feeding tube, with significantly more patients having swallowing problems in the accelerated chemoradiation arm. Such an increase in late toxicity has not been seen when a reduction in the total dose is made using acceleration in combination with chemotherapy.[24] In addition, Denham *et al*. reported that the incidence of a prolonged confluent mucositis, which has been shown to predict for late mucosal reactions, was acceptable.[25]

In our study, significant differences in late effects were noted between the two fractionation schedules [Table 5], indicating that increased dose per fraction (2.75 Gy vs. 2 Gy) influenced late radiation-related morbidity. With a lower biologic dose in terms of late reactions compared with 70 Gy in 35 fractions (using α/β ratio of 3 in linear quadratic model), this hypofractionated schedule was associated with greater long-term toxicity. This, however, needs confirmation through prospectively collected data, particularly randomized controlled trials.

Most of the patients who had loco-regional failure were in the Stage III/IV groups with bulky nodal status at initial presentation. This implies that patients with a large nodal burden are probably less likely to be benefited by hypofractionation. This finding is well-corroborated with MARCH collaborative group meta-analysis, which has shown that the effect of altered fractionation was significantly more pronounced on the primary tumor than on the nodal disease.[4] Rishi *et al.* interpret that patient with nodal size greater than 2 cm × 2 cm had significantly poor DFS with concomitant boost as compared to conventional chemoradiation.[26] We were unable to show a significant difference in OS and DFS. In view of small numbers involved, it would not be correct to draw any definite conclusions regarding local recurrence and survival patterns from this study.

Our study had its share of limitations. It was non randomized, retrospective, with a limited number of patients and short follow-up. There is a lack of human papilloma virus and weight loss data. Though most of our patients had a history of smoking or tobacco-chewing; lack of interpretation these data with the result, still remains one of the major limitations of this study. The follow-up of this study was relatively short and prevent us from commenting on the long-term DFS and OS.

CONCLUSION

We can state that with the caveats of relatively small sample size and limited follow-up, reducing the overall treatment time by increasing dose per fractions while maintaining the BED equivalent to standard fractionation, resulted in comparable tumor control in patients with HNSCC in a resource-limited center. This hypofractionated regimen was associated with an increased but tolerable acute morbidity pattern relative to the conventional schedule, with evidence of increased but manageable late radiation complications. The reduction in number of fractions and overall treatment time allows more efficient use of resources, which can help avoid long waiting times to maximize service productivity, but implementation of this altered fractionation schedule as a routine practice is yet to be established.

REFERENCES

1. James ND, Robertson G, Squire CJ, Forbes H, Jones K, Cottier B, *et al.* A national audit of radiotherapy in head and neck cancer.

Clin Oncol (R Coll Radiol) 2003;15:41-6.
2. Williams MV, James ND, Summers ET, Barrett A, Ash DV, Audit Sub-Committe, Faculty of Clinical Oncology, *et al.* National survey of radiotherapy fractionation practice in 2003. Clin Oncol (R Coll Radiol) 2006;18:3-14.
3. Fowler JF, Harari PM, Leborgne F, Leborgne JH. Acute radiation reactions in oral and pharyngeal mucosa: Tolerable levels in altered fractionation schedules. Radiother Oncol 2003;69:161-8.
4. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, *et al.* Hyperfractionated or accelerated radiotherapy in head and neck cancer: A meta-analysis. Lancet 2006;368:843-54.
5. Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: Three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 2000;355:949-55.
6. Pignon JP, le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4-14.
7. Sanghera P, McConkey C, Ho KF, Glaholm J, Hartley A. Hypofractionated accelerated radiotherapy with concurrent chemotherapy for locally advanced squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2007;67:1342-51.
8. Eisbruch A, Harris J, Garden AS, Chao CK, Straube W, Harari PM, *et al.* Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). Int J Radiat Oncol Biol Phys 2010;76:1333-8.
9. Bakst RL, Lee N, Pfister DG, Zelefsky MJ, Hunt MA, Kraus DH, *et al.* Hypofractionated dose-painting intensity modulated radiation therapy with chemotherapy for nasopharyngeal carcinoma: A prospective trial. Int J Radiat Oncol Biol Phys 2011;80:148-53.
10. Lauve A, Morris M, Schmidt-Ullrich R, Wu Q, Mohan R, Abayomi O, *et al.* Simultaneous integrated boost intensity-modulated radiotherapy for locally advanced head-and-neck squamous cell carcinomas: II – clinical results. Int J Radiat Oncol Biol Phys 2004;60:374-87.
11. Yu E, Shenouda G, Beaudet MP, Black MJ. Impact of radiation therapy fraction size on local control of early glottic carcinoma. Int J Radiat Oncol Biol Phys 1997;37:587-91.
12. Nishimura Y, Nagata Y, Okajima K, Mitsumori M, Hiraoka M, Masunaga S, *et al.* Radiation therapy for T1, 2 glottic carcinoma: Impact of overall treatment time on local control. Radiother Oncol 1996;40:225-32.
13. Agrawal A, deSilva BW, Buckley BM, Schuller DE. Role of the physician versus the patient in the detection of recurrent disease following treatment for head and neck cancer. Laryngoscope 2004;114:232-5.
14. Nakamura K, Kodaira T, Shikama N, Kagami Y, Ishikura S, Shibata T, *et al.* Accelerated fractionation versus conventional fractionation radiation therapy for glottic cancer of T1-2N0M0 Phase III study: Japan Clinical Oncology Group study (JCOG 0701). Jpn J Clin Oncol 2008;38:387-9.
15. Di Nicola L, Gravina GL, Marampon F, Bonfili P, Buonopane S, Di Staso M, *et al.* The impact of conventional or hypofractionated radiotherapy on voice quality and oncological outcome in patients with early glottic cancer. Oncol Rep 2010;24:1383-8.
16. Bibby JR, Cotton SM, Perry A, Corry JF. Voice outcomes after radiotherapy treatment for early glottic cancer: Assessment using multidimensional tools. Head Neck 2008;30:600-10.
17. Carlson DJ, Keall PJ, Loo BW Jr, Chen ZJ, Brown JM. Hypofractionation results in reduced tumor cell kill compared to conventional fractionation for tumors with regions of hypoxia. Int J Radiat Oncol Biol Phys 2011;79:1188-95.
18. Wouters BG, Brown JM. Cells at intermediate oxygen levels can be more important than the "hypoxic fraction" in determining tumor response to fractionated radiotherapy. Radiat Res 1997;147:541-50.
19. Brizel DM, Sibley GS, Prosnitz LR, Scher RL, Dewhirst MW. Tumor hypoxia adversely affects the prognosis of carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 1997;38:285-9.
20. Brown JM. The hypoxic cell: A target for selective cancer therapy – Eighteenth Bruce F. Cain memorial award lecture. Cancer Res 1999;59:5863-70.
21. Brown JM. Exploiting the hypoxic cancer cell: Mechanisms and therapeutic strategies. Mol Med Today 2000;6:157-62.
22. Trotti A, Bentzen SM. The need for adverse effects reporting standards in oncology clinical trials. J Clin Oncol 2004;22:19-22.
23. Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, *et al.* Final results of the 94-01 French head and neck oncology and radiotherapy group randomized trial comparing radiotherapy alone with concomitant radio-chemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004;22:69-76.
24. Staar S, Rudat V, Stuetzer H, Dietz A, Volling P, Schroeder M, *et al.* Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy – Results of a multicentric randomized German trial in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;50:1161-71.
25. Denham JW, Peters LJ, Johansen J, Poulsen M, Lamb DS, Hindley A, *et al.* Do acute mucosal reactions lead to consequential late reactions in patients with head and neck cancer? Radiother Oncol 1999;52:157-64.
26. Rishi A, Ghoshal S, Verma R, Oinam AS, Patil VM, Mohinder R, *et al.* Comparison of concomitant boost radiotherapy against concurrent chemoradiation in locally advanced oropharyngeal cancers: A phase III randomised trial. Radiother Oncol 2013;107:317-24.

Cite this article as: Roy S, Mallik C, Ghorai S, Hazra A, Majumdar A. Hypofractionated versus conventional radiotherapy with or without chemotherapy in head and neck cancer: A comparative study. Clin Cancer Investig J 2015;4:140-6.

Source of Support: Nil, **Conflict of Interest:** None declared.