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A pilot study on feasibility, toxicity and efficacy of novel hypofractionated radiation therapy in advanced non-nasopharyngeal head and neck carcinoma treated with palliative intent

Abstract

Introduction: For palliative treatment in patients with advanced inoperable stage IV head and neck cancer hypofractionated radiotherapy is an efficient, cost-effective option, providing a logistic advantage. Though there are multiple regimens prescribed, no standard of care has been confirmed. In this study, a novel hypofractionated regimen has been tested for feasibility and toxicity along with an assessment of objective treatment response and survival along with self-reported quality of life.

Patients and methods: 30 Patients, having pathologically proven advanced and metastatic non-nasopharyngeal squamous cell carcinoma of Head and Neck (Stage IV) attending the Radiotherapy Department of Hospital were allocated to the prescribed hypofractionation regime with 35 Gray in 7 fractions, given as 2 days a week (total 3.5 weeks). In patients with good response and tolerability, 10 Gray boosts in 2 fractions were given. Patients were followed up at regular intervals for at least 1 year.

Results: The regimen faced a 97% treatment completion rate. Mean time to completion (from first contact) is 5.8 (95% CI = 5.7–6.0) weeks. The toxicity of this treatment regimen was tolerable with 23.3% acute and 33.3% incidence of chronic grade 3/4 toxicities. Objective response rate of this study was 66.7% ($p = 0.001$) with further 16.7% patients having stable disease. After one month of treatment significant improvement of quality of life was reported in terms of global health score, functional score and symptoms score. Mean progression-free survival is 34.4 (95% CI = 27.8–41.1) weeks with 49.4 (95% CI = 44.3–54.5) weeks of overall survival in 1 year follow up period.

Conclusions: The regimen is well tolerated and is highly feasible and has provided a good response rate and improved quality of life immediately after treatment along with a better one-year overall survival rate.

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Key words: palliative radiotherapy, hypofractionation, pilot study, head and neck cancer, quality of life, feasibility trial

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Introduction

Overall, 57.5% of global head and neck cancers occur in Asia, especially in India. Head and neck cancer in India accounted for 30% of all cancers, whereas 60–80% of patients present with the advanced disease which is often beyond the scope of curative treatment by surgery or chemoradiation [1]. Population-based cancer registry in India projects that the number of tobacco-related cancer and head and neck cancer should be 3,16,734 and 2,18,421, respectively, by 2020 [2]. In most cases, due to extensive locoregional involvement, poor general condition of the patient, or comorbid conditions curative treatment is not possible. The overall 5-year survival for the advanced stages is approximately 50% and disappointingly, this has not markedly improved in the last decades, because patients frequently develop relapse at the primary site, distant metastases and second primary tumour (SPT) [3]. Therefore, the relevance of aggressive treatment in unresectable locally advanced head and neck cancer has been questioned. The intent of treatment in such cases is to improve the quality of life of the patients, keeping their socioeconomic condition in mind and judiciously utilizing the precious resources for curable conditions [4].

In most cases, the aim of treatment of stage IV head and neck cancer is palliation. In stage IV A and B, concurrent chemoradiation therapy has a cure rate of only 10–30% and a 5-year survival rate is 17% [5, 6]. Although some stage IVA or IVB patients benefit if they are operable, unresectable or inoperable patients have very low overall survival and poor quality of life. The standard treatment for unresectable advanced head and neck squamous cell carcinoma is chemo-radiotherapy, which can be toxic, particularly among patients with coexisting medical conditions [7]. Furthermore, patients who are unable to attend a hospital daily on long-term radiotherapy regimes face difficulties regarding compliance and completion of such therapy resulting in a poor outcome. Additionally, acute toxicities of the standard chemotherapeutic protocols have worsened the risk-benefit ratio, adding to social, personal and economic adversities, amounting to an immense disease burden. A study by Smith and Smith infers that the logistic challenges of radiation treatment delivery in a frail patient should be of concern, especially in patients with limited expected survival, the risk-benefit assessment must weigh the expected survival gain from radiation treatment against the time spent on the treatment itself [8].

Hypofractionated radiotherapy provides effective palliation of symptoms. Most of the studies that discussed the provision of hypofractionated radiotherapy to very advanced head and neck cancer showed at least comparable or better outcomes than conventional fraction radiotherapy regarding the quality of life and toxicity profile [9–13]. However, in standard hypofractionation regimens, the treatment is usually delivered five days a week which is mostly given on a daycare basis. The current study explored the feasibility and outcome of a twice-weekly regimen that delivers an adequate radiotherapeutic dose but causes minimal possible inconvenience/ toxicity to patients with the intent of best possible palliation.

Patents and methods

Sampling design

This is a single institutional, single-arm, prospective, interventional, open level, cohort, non-randomized pilot study, similar to a phase II trial, revealing efficacy and toxicity of the proposed treatment plan. The recruitment to treatment was started in January 2017 and the patients were recruited as per convenience sampling as they visited the Radiotherapy OPD of the Hospital. The last recruitment that has been included in the study was in August 2018. Patients were being further recruited in this protocol for extending the study and planning of a future randomized trial, however, not included in this study since the preliminary outcomes were planned to be reported after a follow-up period was of one year (12 months). A total of 48 patients with inoperable stage IV disease were screened with the following inclusion criteria: age more than 18 years with histopathologically/cytopathologically proven squamous cell carcinoma of head and neck excluding nasopharynx (stage IV disease) who were declared inoperable and those who had ECOG performance status ≤ 2 [14] without any uncontrolled comorbidity. This study protocol was approved by an Institutional Ethical Committee and the study was conducted in accordance with the Declaration of Helsinki. Informed consent was taken from all patients included. Patients with prior radiotherapy, chemotherapy or definitive surgery (except laser surgery) for the present disease and pregnant and lactating mothers were excluded. Finally, 30 patients were analysed for the outcome. The flow diagram has been depicted below for a clear understanding of the study proceedings (Fig. 1) [15].

Treatment Protocol

All patients were treated with EBRT (external body radiation therapy) through Bhabatron II Co^{60} machine with a teletherapy dose of 35 Gy in 7 fractions every Wednesday and Saturday. In patients who were found to have good clinical re-

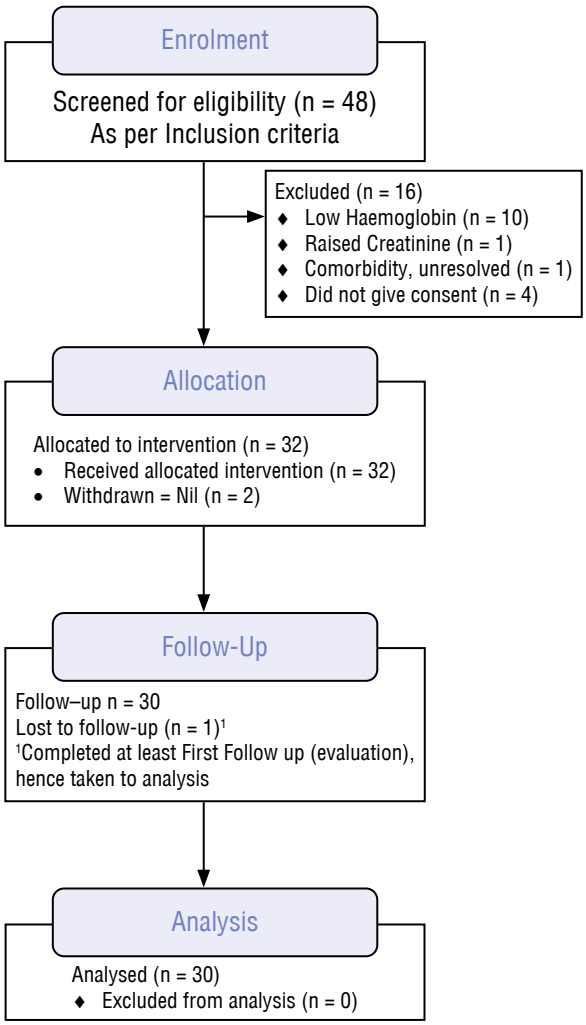

Figure 1. CONSORT flow diagram of the study

sponse were administrated 2 more fractions with cord sparing. CT scan (Philips® Brilliance CT simulator) based simulations were done using dual-mode (0 and 90 deg) surview and 3 mm axial cut images and treatment was planned using planning technique through TPS (Oncentra ™ ver. 4.5.3). In the first phase, the total dose was 30 Gray in 6 fractions. Later, after keeping the spinal cord off the field, the remaining doses were given. The dose planning is depicted in Figure 2. All patients other than the maxillary antrum subsite were treated with two lateral opposed rectangular fields prescribing the dose at the midplane between the two lateral field planes irrespective of the laterality of the tumour. Such field planning was done for both phases of treatment. For the maxillary antrum patients in three of the four patients, the CTV1 did not cross the midline. These patients were treated with wedge paired anterior and lateral fields. A sample plan is shown in Figure 3.

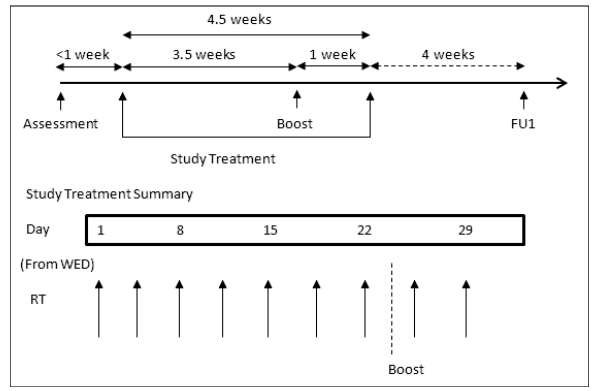

Figure 2. Outline of the treatment

Assessment and data collection

At pre-treatment assessment, demographic variables, tumour parameters, variables critical in depicting the patient's status before treatment, and quality of life items including the 65-point questionnaire bearing the Likert scale were included. During the treatment phase, variables related to toxicity are included according to RTOG CTCAE criteria ver 4.0 [16]. In the follow-up phase, the first follow–up was most important to assess treatment response, bearing the RECIST criteria (Objective, ordinal scale) [17]. Before the beginning of treatment and after one month of completion quality of life (QoL) was assessed as per the EORTC QLQ H&N35 questionnaire. The scaled items were linearly transformed as per the guideline [18].

Statistical methods

Analysis of data has been done using software-assisted statistical tools, namely, IBM SPSS version 23.0 and STATA SE 13. Both descriptive and causal analyses are done including survival studies. Quantitative methods include descriptive analysis, comparison of means, proportional z test, Fisher exact test, Kaplan Meir survival analysis and paired t-test for pre-and post-treatment change in QoL. Survival analysis includes progression-free survival and overall survival. A p-value of less than 0.05 is taken as a significant difference (alternate hypothesis being true).

Results

Demographic and disease characteristics

Patients included in the study have ages ranging from 42 years to 68 years, with a median age of 61 years. A significantly higher ($p = 0.035$) male preponderance is seen. Major disease subsites are oral cavity (23.3%), oropharynx (16.7%), supraglottic larynx (13.3%), larynx (10%), subglottic larynx and hypopharynx (26.7%) and maxillary sinus (10%). Overall, 36.7%

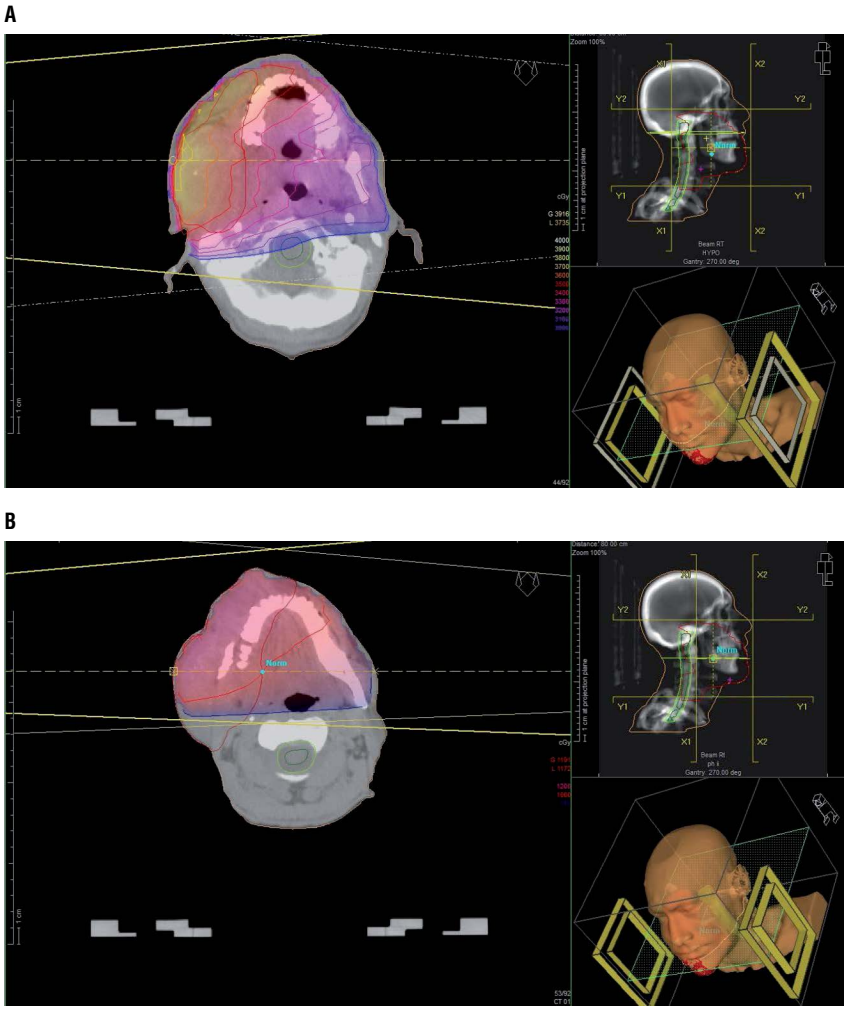

Figure 3. Sample Field plan: **A.** Phase I. **B.** Phase II. Cord off

of patients have stage IVA, 46.7% have stage IVB disease and 16.6% patients have stage IVC (metastatic) disease. 16.7% of patients have a well-differentiated tumour, 46.7% are moderately differentiated and the rest have poorly differentiated tumours (Table 1).

Feasibility and toxicity of treatment

All 30 patients completed the primary phase of treatment. Only one patient could not be given the boost phase due to poor response and disease progression during the treatment. The mean time to complete the treatment including boost was 5.8 weeks (95% CI 5.74–6.01 W) with a minimum time of 5.5 weeks and a maximum time of 6.5 weeks from the period of first contact. The mean follow-up period was 49.4 weeks (95% CI= 44.3–54.5 weeks), with an attempted minimum 1-year follow-up to measure a 1-year survival rate (Table 2).

Among the patients treated, 7 patients (23.3%) suffered from grade 3 or 4 acute toxicity, which is proportionally low ($p < 0.001$). The mean time to produce clinically detectable toxicity is 5.9 weeks (95% CI 4.7–7.3 weeks), with a minimum time of 1 week and a maximum of 20 weeks. Grade 3 or 4 late toxicity was seen in 10 patients (33.3%). A Fisher exact test has been done to measure the significance between the occurrence of high-grade toxicity in the acute and late settings, which has come to be insignificant ($p = 0.57$). Acute skin toxicity has been found to be non-severe. No patient was suffering from Grade 4 toxicity and only 1 patient was found to have Grade 3 skin toxicity. However, significantly higher proportions of patients suffered from high-grade acute dysphagia of whom 2 (6.7%) had grade 4 and 4 (13.3%) had grade 3 disease. 2 patients had early mortality, before falling in the time criteria for producing late toxicity. Hence, late toxicities are measured on 28 patients. Among them, no patient had grade 4 skin toxicity and 1 patient had grade 3 skin toxicity. Prolonged or late-onset grade 3 dysphagia was seen in 3 (10%) and grade 4 in 1 (3.3%) patients. 15 (50%) patients had grade 1 dysphagia. Radiation-induced late spinal cord toxicity was seen only in 2 patients, both of whom had grade 1 disease (Table 3).

Table 1. Patient characteristics

Characteristic	Number of Patients (Percentage) N = 30	P-value
Age Group		
< 50 years	4 (13.3)	
50–60 years	11 (36.7)	0.09
> 60 years	15 (50)	
Sex		
Male	22 (73.3)	**0.035**
Female	8 (26.7)	
BMI		
Underweight	5 (16.7)	**0.015**
Normal Range	19 (63.3)	
Overweight	6 (20)	
ECOG PS		
PS1	9 (30)	**0.002**
PS2	21 (70)	
Tumour Site		
Oral Cavity	7 (23.3)	
Oropharynx	5 (16.7)	
Supraglottic Larynx	4 (13.3)	
Larynx	3 (10)	0.593
Subglottic larynx and Hypo-pharynx	8 (26.7)	
Maxillary Sinus	3 (10)	
Tumour Grade		
Well Differentiated	5 (16.7)	
Moderately Differentiated	14 (46.7)	0.31
Poorly Differentiated	11 (36.7)	
Tumour (T) Stage		
T2	4 (13.3)	
T3	3 (10)	0.06
T4a	13 (43.3)	
T4b	10 (33.3)	
Nodal (N) Stage		
N1	6 (20)	
N2	17 (56.7)	0.075
N3	7 (23.3)	
Metastasis (M) Stage		
M0	25 (83.3)	**0.002**
M1	5 (16.7)	
TNM Stage		
Stage IVA	11 (36.7)	0.19
Stage IVB	14 (46.7)	
Stage IV C	5 (16.7)	
Main Symptom		
Pain	11 (36.7)	
Dysphagia	8 (26.7)	0.29
Swelling	8 (26.7)	
Others	3 (10)	
Disease Feature		
Exophytic Swelling	18 (60)	0.37
Ulceroproliferative	12 (40)	

Treatment response and outcomes

The treatment resulted in 3.3% complete response (of 1 patient) on initial follow-up and 63.3% partial response. 5 patients (16.1%) had stable disease and 5 patients had progressive disease despite treatment. The incidence of partial response has a significantly higher occurrence ($p = 0.001$). 11 (36.7%) death events occurred during the follow-up, which is significantly high in proportional expectancy for no death ($p = 0.003$). The mean time to progression is 34.4 weeks (95% CI = 27.8–41.1) and overall survival is 49.4 weeks (95% CI = 44.3–54.5) (Table 4). Overall survival is better in the set showing a 63.3% one–year survival rate. The Kaplan-Meier survival estimates are shown in curves below, shaded area depicting 95% confidence interval (Fig. 4)

There has been a significant betterment of QoL. A highly significant increase in Global health scores and overall symptom scores have been observed. Dysphagia scores only improved modestly but significantly ($p = 0.035$). Table 5 summarises the QoL status before and after treatment.

Discussion

The challenge of cancer treatment is not only limited to the improvement or cure of the disease but also to giving relief to the suffering, ensuring comfort and dignity by addressing, assessing and diminishing pain and other morbidities, including psychosocial and spiritual issues [19]. In inoperable very advanced head and neck cancer, palliative radiotherapy has an immense impact and is nowadays an important field of research. Constructing a novel palliative radiation regimen is challenging and is not free of hazards. The goal of such studies is not limited to assessing the

Table 2. Parameters of feasibility and toxicity

Determinants	Value (%)	Significance
Time to completion	Mean 5.8 weeks	(95% CI 5.7–6.0 weeks)
	(Range 5.5–6.5 weeks)	
Time to Follow Up	Mean 49.4 weeks	(95% CI 44.3–54.5 weeks)
	(Range 16–70 weeks)	
Acute toxicities (cumulative)		
No Grade 3/4 toxicity	23 (76.7)	
Grade 3/4 toxicity	7 (23.3)	**P < 0.001**
Time to produce toxicity	Mean 5.9 weeks	(95% CI 4.7–7.3 weeks)
	(Range 1–20 weeks)	
Late toxicities (cumulative)		
No Grade 3/4 toxicity	20 (66.7)	
Grade 3/4 toxicity	10 (33.3)	**P = 0.01**
Non Parametric difference		
Acute vs. Late toxicities in grading	(Fisher exact test)	P = 0.57

Table 3. Incidence of acute and late toxicities

Acute toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	P-value
Skin	1 (3.3)	10 (33.3)	18 (60)	1 (3.3)	0 (0)	**< 0.001**
Mucosa	0 (0)	8 (26.7)	18 (60)	3 (10)	1 (3.3)	**0.001**
Dysphagia	0 (0)	10 (33.3)	14 (46.7)	4 (13.3)	2 (6.7)	**0.021**
GI toxicities	0 (0)	12 (40)	16 (53.3)	1 (3.3)	1 (3.3)	**< 0.001**
Neutropenia	24 (80)	6 (20)	0 (0)	0 (0)	0 (0)	0.053
Anaemia	5 (16.1)	11 (36.7)	14 (46.7)	0 (0)	0 (0)	0.72
Late toxicity	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**P value**
Skin	0 (0)	17 (56.7)	10 (33.3)	1 (3.3)	0 (0)	**< 0.001**
Mucosa	0 (0)	12 (40)	10 (33.3)	5 (16.7)	1 (3.3)	**0.03**
Dysphagia	0 (0)	15 (50)	9 (30)	3 (10)	1 (3.3)	**0.004**
Xerostomia	12 (40)	13 (43.3)	3 (10)	0 (0)	0 (0)	**0.002**
Myelopathy	26 (86.7)	2 (6.7)	0(0)	0 (0)	0 (0)	–
Laryngeal	11 (36.7)	12 (40)	4 (13.3)	1 (3.3)	0 (0)	**0.0016**

improvement of quality of life, whereas, like any phase II trial this should explore the occurrence of toxicity and evaluate the treatment response as well [20]. The trouble of unequal distribution of BED, re-oxygenation, vascular endothelial cell death and anti-tumour immunity complicates the situation [21]. But, in a large tumour mass, which may also be nodal, hypofractionated radiotherapy with discrete avoidance of critical structure may be of important value in reducing the tumour size especially with necrosis and poor oxygenation.

The BED of this new fractionation regimen has come out to be 52.5 Gray without boost and 67.5 Gray with boost, which is not very inferior to 79.2 Gray of BED in standard EQD2 of 66 Gray. Also, this regimen has a superior BED than the regimen used in the Hypo trial (48 Gray), the trial by Das et al. (56 Gray) and the much-discussed Christie Scheme (65.63 Gray) [11, 13, 22]. Moreover, the BED to late reacting tissue and normal tissue were 93.33 Gy without boost and 120 Gy with boost. Only the Hypo trial had a boost phase and BED to late reacting tissue was 108 Gy. That of conventional fractionation comes out to be 110 Gy in 66 Gy dose and 116.7 Gy in 70 Gray dose, which is 102.1 Gy in the Christie Scheme. Hence, the probable toxicity to normal tissue is comparable

Table 4. Response and outcomes of the treatment

Parameters	Values	P-Value
Objective Response Rate		
No response	10 (33.3)	
Response		
CR	1 (3.3)	
PR	19 (63.3)	**P = 0.001**
SD	5 (16.7)	
PD	5 (16.7)	
Time to Progress	Mean 34.4 Weeks	(95% CI = 27.8 – 41.1W)
Death Event		
Living till last follow up	19 (63.3)	**0.003**
Death/ Lost to follow up	11(36.7)*	
Overall Survival	Mean 49.4 Weeks	(95% CI = 44.3 – 54.5W)

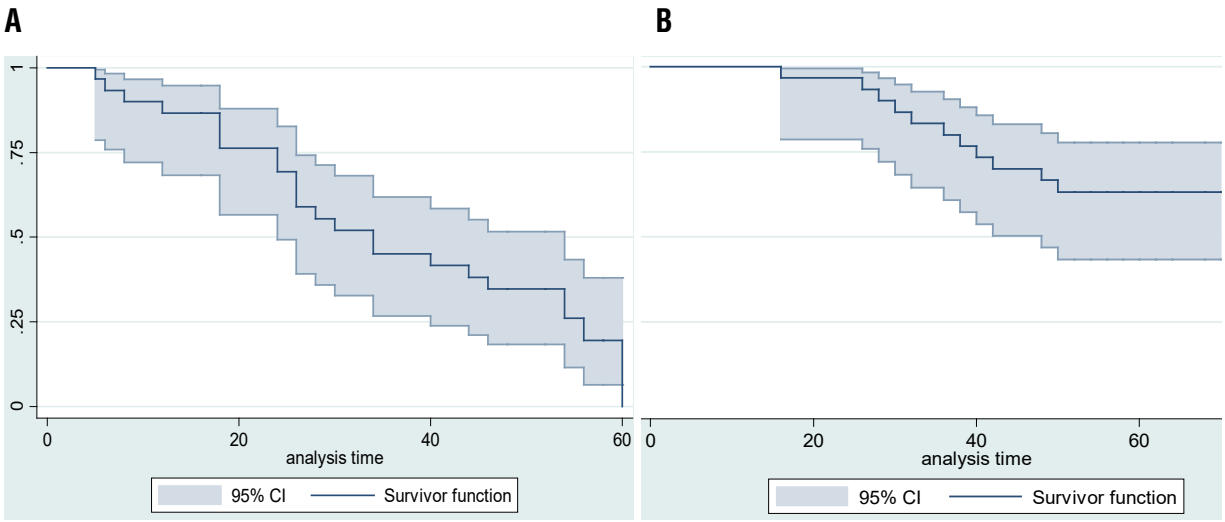

Figure 4. Kaplan Meier survival estimates of **A.** 1 year PFS, **B.** 1 year OS with 95% CI (time estimates in weeks)

Table 5. Self-reported QoL scores before and after treatment

Variable	Score before	95% CI	Score after	95% CI	Sig.
Global Health Score	40.01	32.45–47.56	63.15	51.47–74.83	**< 0.001**
Functional Score	47.22	36.85–57.58	67.6	56.22–79.02	**.009**
Overall Symptoms Score	62.87	55.91–69.83	43.15	33.05–53.25	**< 0.001**
Head and Neck Symptoms Score	69.16	60.14–78.18	43.18	29.76–56.61	**< 0.001**
Dysphagia Score	65.87	55.91–75.84	52.13	41.46–62.80	**.035**

or only modestly high, indicating in the theoretical background the feasibility of this novel fractionation should have been highly probable. It is also an advantage that the paucity of high-risk normal tissue helped to mitigate the biological dose discrepancies arising while administering this fractionation. Additionally, the total number of patient contacts in this study is 9 including the boost phase, which is lower than both Christie Scheme and the study by Das et al. [11, 22]

Apart from palliation with the intent of good response and minimal toxicity, this study also has values related to treatment compliance and economic

aspects of radiation therapy. As being a busy government-run institute, the place of the current study must prioritize patients for treatment with radiation therapy. Hypofractionated radiation therapy presents patients with umpteen benefits. Reduced waiting time, infrequent visits and increased time for recovery are among them.

To assess toxicity profile was an important primary endpoint for this study. However, this study had no toxicity-related non-completion of treatment. Two other major studies by Ghosal et al. [23] and Das et al. [22] also had limited toxicity in a hypofractionated palliative regimen. The feasibility of this palliative regimen is highly dependent on the acute and late toxicity profile of the recruited patients [24]. In the former study, no patient had grade 3 mucositis out of 25 patients [23] and later had 6 patients with grade 3 mucositis out of 33 samples. A major Indian study; Agarwal et al. [25] had acceptable acute and late reactions while treating with 40 Gy. dose in 16 fractions.

A recent study by Al-Mamgani et al shows a regimen of 36 Gy in 6 fractions given twice a week has a similar outcome as compared to a longer hypofractionated regimen but less grade 3 mucositis [26]. In the current study, the incidence of dermal toxicity is very low, whereas grade 3 or higher dysphagia was the most dreaded toxicity. As there was a high number of recruits who already suffered from dysphagia, the spectrum of acute toxicity has been merged with already set in symptoms. In the current study, there was no toxicity-related withdrawal or premature termination of therapy observed. According to classical radiobiology teaching, hypofractionated radiotherapy should carry a higher risk of late toxicity [27]. As, modern studies also show linear-quadratic model holds good even in a very high dose per fractionation, which may be as high as 10 Gy per fraction, the calculation of radiation dose to the tumour and normal tissue should be valid with a standard formula [28]. The twice-weekly regimen used in this study might be helpful in normal tissue repair probability, which is more than that of the tumour. However, trials show that if survived, late toxicities gradually wear off after 1 to 2 years [29].

Most of the researchers have put the treatment response as the primary endpoint of their study. The quad shot regimen which used 14 Gy. of the total dose given in 4 fractions over 2 days reported 53% objective response with median progression-free survival of 3.1 months [9]. Further studies by Chaudhury et al (2020) on the comparative outcome of Quad Shot with a longer Hypofractionation regimen showed it fared well in terms of toxicity [30]. The trial by Mohanty et al. yielded 37% partial response at 1 month. The study by Das et al. [22] had a median survival of 7 months with a median follow-up period of 6 months (range 1 to 26 months). Compared to the present literature, thus, in terms of treatment response, the present study shows great promise. However, 80% of patients had disease progression during the period of assessment, but the median time to progress is 35 weeks, which is close to the median follow-up period. Hence, it might be concluded that although the treatment regimen has a good clinical response, progression at around one year is almost a rule. Grewal et al. concluded that the shorter courses are better in patients with limited life expectancy, however, they should be chosen as a multiparty approach involving all stakeholders [31]. A systematic review by Fabian et al. stated 90% of the palliative radiation studies in head and neck cancer fail to show patient-reported outcomes [32]. Advantageously the current study quantitatively assessed QoL and the improvement showed by the present regimen is promising.

The main limitation of the study is the small sample size and being a single institutional study. The pilot study, however, has proved good feasibility and manageable toxicity of the treatment regimen, there is a scope of a larger randomized controlled trial using this regimen.

Conclusions

This novel hypofractionation scheme has good feasibility with acceptable toxicity and good treatment response in terms of disease control and survival, though a high incidence of disease progression after an interval. However, the excellent outcome regarding the improvement of quality of life, both in perceived and objective assessment, renders this treatment regimen worthy to be used as palliative therapy in stage IV inoperable non-nasopharyngeal head and neck cancer.

Declaration of conflict of interests

The authors declare that there is no conflict of interest.

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