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Original Article

TO STUDY PALLIATION OF SYMPTOMS BY A HYPOFRACTIONATED RADIOTHERAPY SCHEDULE IN ADVANCED INOPERABLE SQUAMOUS CELL CARCINOMAS OF THE ORAL CAVITY

MUNAGAPATI VISHNU PRIYA, BEEREDDY KARTHIK REDDY, KADARLA KRISHNA, PONUGOTI SUDHARANI, MALLADI RAMAKRISHNA

Department of Radiational Oncology, MNJ Institute of Oncology and Regional Cancer/Osmania Medical College, Hyderabad, Telangana, India.

***Corresponding author: Dr. Ponugoti Sudharani. Email: drponugotisudharani223@gmail.com**

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ABSTRACT

Objective: The aim of the study was to study palliation of symptoms and improvements in quality of life (QoL) in inoperable squamous cell cancers of the oral cavity with a hypofractionated radiotherapy schedule.

Methods: It is a prospective and observational study in patients with locally advanced squamous cell cancers of the oral cavity attending the outpatient clinic who have been deemed inoperable after discussion in a multidisciplinary team were considered. The data was tested using Friedman's test for the significance in QoL.

Results: All of the functional scales were found significant in this study with physical functioning, emotional functioning and cognitive functioning (CF) being significant at 1% alpha level while role functioning (RF) and social functioning (SF) are significant at 5% alpha level. RF was assessed based on the capabilities of the patient to finish daily activities. The median score remained at 33 but the interquartile range (IQR) was showing an increasing trend. Both pain and head-and-neck specific pain had significantly reduced over time. Fatigue had shown a constant reduction during radiation and during the first follow-up as well. The increase in nausea, vomiting, and constipation during radiation can be attributed to the use of morphine during radiation for pain control and as an effect of radiation itself. There was weight loss during radiation which improved during subsequent follow-up visits.

Conclusions: In patients diagnosed with inoperable oral cavity cancer, hypofractionated radiotherapy delivering 50 Gy in 20 fractions over 4 weeks is a well-tolerated and safe regimen. In our study, statistically significant QoL improvement in global health score, SF, and CF lasting for a minimum of 6 weeks was attained after completion of treatment with this regimen.

Keywords: European organization for research and treatment of cancer, Quality of life questionnaire, Eastern cooperative oncology group, Physical functioning, role functioning, Emotional functioning, Cognitive functioning, Social functioning.

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INTRODUCTION

Oral cavity malignancies present in locally advanced stages more often in our setting. Surgical management is not feasible in such patients. Palliation becomes the main intent of treatment as the survival is low. Palliation can be achieved with either radiotherapy or chemotherapy, although chemotherapy alone has limited benefits in these situations.

It is recognized that palliative radiotherapy provides an improvement in quality of life (QoL) along with palliation in incurable malignancies. Pain, dysphagia, odynophagia, cough, and respiratory distress are some of the symptoms commonly associated with oral cavity malignancies [1,2].

Decisions regarding optimal integration of surgery, radiation, and chemotherapy should be made on a case-to-case basis in a multidisciplinary tumor board setting. Treatment planning of advanced oral cavity cancers is derived from trials that included a heterogeneous group of patients which included all head-and-neck sites and observational data from the oral cavity cancer patient series. A surgeon, a radiation oncologist, and a medical oncologist should see the patient before deciding on a treatment strategy. Various tumor factors, patient factors, and functional outcomes of treatment, as well as the expertise of the treatment team and availability of treatment delivery techniques, are to be considered in forming an individualized treatment plan. In head-and-neck cancers, early oral cavity cancer (Stages I and II) is treated with single modality surgery or brachytherapy with similar 5-year survival rates of 80–85%. In India, majority of the patients present in a locally advanced stage, needing a multimodality treatment. In tsage III and IV disease, surgery followed by radiotherapy with or without radiotherapy is the preferred approach [3,4].

Standard definitive radiotherapy regimens use 1.8–2 Gy per fraction for 5 days a week for 30–35 fractions depending on the adjuvant or radical setting. In palliative radiotherapy, the main aim of treatment is symptom control rather than cure. To reduce the overall treatment time hypofractionated schedules are used, where the dose per fraction will be more and the duration of treatment is less than in comparison to conventional schedules. Palliation of symptoms with a palliative radiotherapy regime is the main objective of the study. Quality of life questionnaire (QLQ) were conducted to assess the subjective symptoms and QoL. The questionnaires used are European organisation for research and treatment of cancer (EORTC) QLQ-C30 and EORTC QLQ-HandN35. Tumor response was documented based on clinical assessment. Our aim is to study palliation of symptoms and improvements in QoL in inoperable squamous cell cancers of the oral cavity with a hypofractionated radiotherapy schedule.

METHODS

It is a prospective and observational study done in the department of radiotherapy from December 2020. Date of ending: September 2022.

Patients with locally advanced squamous cell cancers of the oral cavity attending the outpatient clinic at MNJ Institute of Oncology and Regional Cancer Center who have been deemed inoperable after discussion in a multidisciplinary team were considered. Patients fulfilling the inclusion criteria were enrolled in the study after informed consent.

Inclusion criteria

Age in between 18 and 70 years surgically unresectable biopsy-proven squamous cell carcinomas of the oral cavity with clinical involvement of infratemporal fossa, fixed nodes, or extensive skin involvement with or without cutaneous nodules or severe trismus, stage IV-A, IV-B with significant comorbidity, stage IV-C for palliation of local symptoms, and ECOG performance score 0–2 were included in the study.

Exclusion criteria

The previous history of radiotherapy in head-and-neck malignancy was excluded from the study.

The flow of the study

Locally advanced, biopsy-proven squamous cell carcinomas of the oral cavity which are deemed inoperable and the intent of treatment is palliation are enrolled for the study.

After the patient selection is done, initial assessment of the symptoms and the QoL are done before starting treatment with EORTC QLQ-C30 and EORTC-HandN35 questionnaires (Tables 1 and 2). The patients answered the questionnaire on their own.

Treatment with radiotherapy at a dose of 50 Gy in 20 fractions at 2.5 Gy per fraction with 5 fractions per day for a total duration of 4 weeks is started.

Weekly assessments of patients for toxicities were done using the CTCAE v5.0.

Questionnaires were again answered by the patients at the end of the treatment. Patients are advised on post-treatment care and advised to review at the outpatient clinic after 6 weeks (Table 3).

During the first follow-up, that is, after 6 weeks, the patients are clinically assessed and are again encouraged to fill in the questionnaire (Tables 4 and 5).

Patient workup and planning

Patients who fulfilled the inclusion criteria were enrolled in the study after getting informed consent and underwent the following steps in sequence; detailed history taking followed by thorough general, systemic, and local examination and investigations.

Radiation therapy planning and treatment delivery included the following steps in sequence

1. Positioning and Immobilization
2. Simulation
3. Dose prescription and treatment planning techniques and plan finalization
4. Treatment delivery.

Patient positioning and immobilization

The patient was positioned supine with arms by the side and was immobilized using a thermoplastic mask.

Simulation

The patient is simulated on a wide-bore CT machine which directly feeds the images to the planning system.

Dose prescription and planning

Parallel opposed lateral technique is used to treat the disease. Field borders are adjusted so as to include the gross nodes with a margin of up to 2 cm wherever feasible.

Field size, treatment distance, beam energy, beam direction, weighting, and beam modification devices used during each treatment session are calculated and provided to technologists for treatment delivery. Patients were treated on a clinac 600-c machine. All patients were treated for 50 Gy in 20 Fractions with 2.5Gy per fraction with one fraction per day (5 fractions per week) lasting for 4 weeks. The posterior margin of the fields is brought anterior to the mid portion of vertebral bodies to spare the spinal cord. All the patients undergoing treatment were assessed weekly and treated symptomatically whenever necessary. Palliative care physicians were consulted regarding pain management in required patients.

Statistical Analysis

The data analysis was done using Microsoft Excel software. Mean, median, and standard deviation were used to represent the outcome of variables. The data were tested using Friedman's test for the significance in QoL.

RESULTS

A total of 30 patients were enrolled in this prospective and observational study after getting informed consent.

All the patients completed the radiotherapy schedule. The median duration of the course was 28 days. Twenty-one patients completed the radiotherapy schedule within 4 weeks. Nine patients had to take breaks, the most common cause being Grade 3 mucositis. Twelve patients required admission to the hospital for pain management and G-CSF for mucositis.

Toxicities were more profound in the 3rd and 4th weeks of radiotherapy. All the patients received appropriate symptomatic care.

During the post-radiotherapy assessment, the patients who had partial response constituted 93.3% of the initial sample size (28/30). Two patients had stable disease. Of the 30 patients enrolled in the study, 3 patients did not report for the first follow-up. One patient had died and two others were lost to follow-up. During the first follow up, 22 (73.3%) patients had partial response 3(10%) patients had stable disease and 2(6%) patients had progressed.

Fatigue, vomiting, pain, insomnia, and constipation are significant symptoms according to EORTC QLQ-30 symptom scales.

Pain, swallowing, social eating, social contact, difficulty opening mouth, dry mouth, and sticky saliva are significant symptoms according to QLQ-HandN35 symptom scales.

All of the functional scales were found significant in this study with physical functioning (PF), emotional functioning (EF), and cognitive functioning (CF) being significant at 1% alpha level while role functioning (RF) and social functioning (SF) are significant at 5% alpha level. RF was assessed based on the capabilities of the patient to finish daily activities. The median score remained at 33 but the IQR was showing an increasing trend (Figs. 1-5).

DISCUSSION

In this study, palliation of symptoms in inoperable squamous cell cancers of the oral cavity by a hypofractionated palliative radiotherapy schedule has been evaluated using validated QoL tools. Our study population consists of 30 inoperable oral cavity cancers, who were recruited after getting informed consent, over a period of 22 months.

Most of the studies on palliative radiotherapy in the head-and-neck included all the subsites of the head and neck. The most common site in the majority of the studies was the oral cavity, especially in Indian studies. Hence, we planned to study oral cavity cancers alone. Among the study population, the tongue was the most common subsite. The stage and histology were similar to other studies which included Stage IVA and squamous cell carcinoma. As seen in other studies, there was male predilection which can be attributed to exposure to risk factors

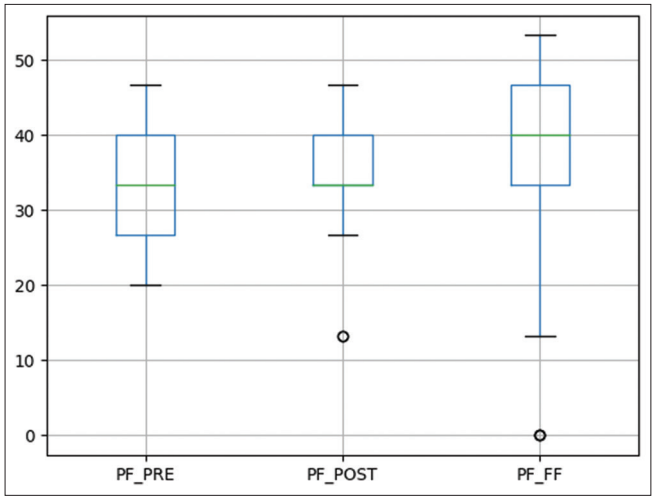

Fig. 1: Box plot showing the variation in physical functioning score over the course of the study

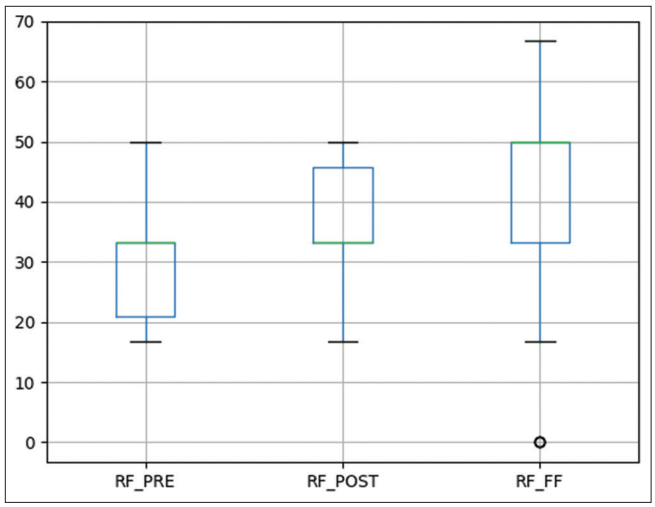

Fig. 2: Box plot showing the variations in role functioning score over the course of the study

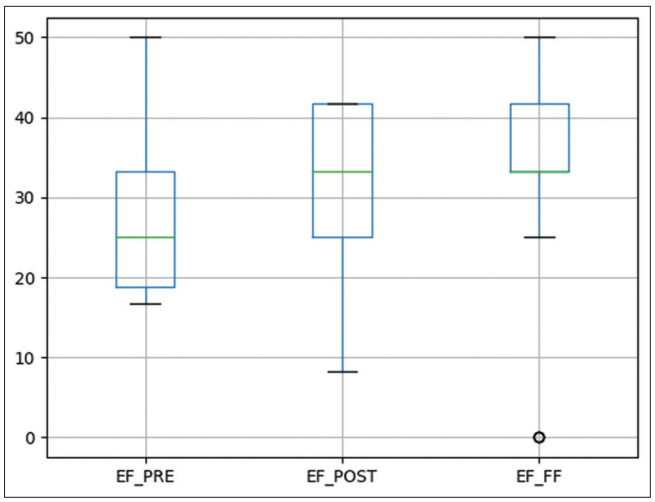

Fig. 3: Box plot showing variations in emotional functioning score over the course of the study

like tobacco and alcohol. Among the male patients, most were using tobacco either in the form of smoking or smokeless or both. Contrary to western literature where smoking forms the major risk factor, ICMR data addresses smokeless tobacco as a high-risk factor for oral cavity cancers in India [4,5].

Most of the patients in our study were treated with two dimensional conventional parallel opposed lateral technique on a clinac 600-c machine. The use of conformal radiotherapy andintensity-modulated

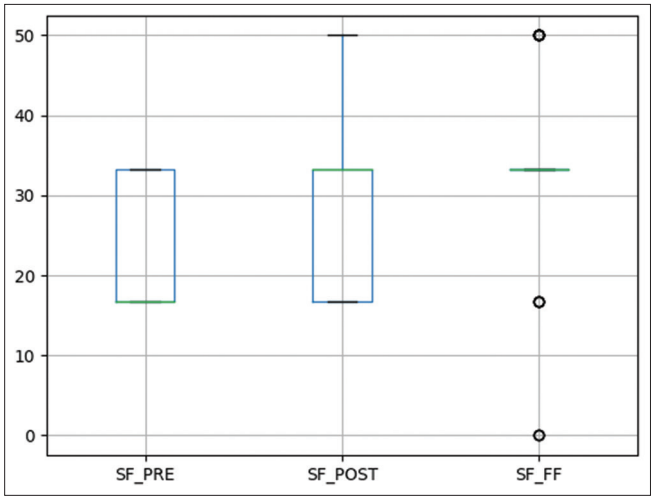

Fig. 4: Box plot showing variations in social functioning score over the course of the study

Table 1: Patient demographics

Variable	Number of cases
Age	52 (27–64)
Gender	
Male	22 (73.3)
Female	8 (26.7)
Risk factors	
Alcohol	15 (50)
Tobacco	25 (83.3)
Site	
Tongue	8 (26.7)
Floor of mouth	4 (13.3)
Buccal mucosa	13 (43.3)
Retromolar trigone	2 (6.7)
Alveolus	3 (10)
TNM	
T4	30 (100)
N0	5 (16.7)
N1	12 (40)
N2	11 (36.7
N3	2 (6.6)

Table 2: Toxicities during radiotherapy (CTCAE v5.0)

Toxicity	Grade 2	Grade 3	Grade 4
Mucositis	19	11	Nil
Dermatitis	14	9	Nil
Dysphagia	16	13	Nil
Xerostomia	18	11	Nil

Table 3: Response assessment

Clinical response	End of radiotherapy	First follow-up
Complete response	Nil	Nil
Partial response	28	22
Stable disease	2	2
Progressive disease	Nil	3

Table 4: Descriptive analysis of European organization for research and treatment of cancer quality of life questionnaire-30 symptom scales over time

Domain	Pre	Post	FF	Pre	Post	FF	p-value
Fatigue	74.1 (11)	66.7 (6.5)	58.9 (9.7)	77.8 (66.7–77.8)	66.7 (66.7–66.7)	55.6 (55.6–66.7)	0.000
Vomiting	30.5 (13.2)	52.2 (17.9)	11.1 (9.2)	33.3 (16.7–33.3)	50 (37.5–66.7)	16.7 (0–16.7)	0.000
Pain	78.34 (16.4)	68.9 (11.3)	57.4 (12.5)	75 (66.7–95.8)	66.7 (66.7–66.7)	66.7 (50–66.7)	0.002
Dyspnea	4.4 (11.5)	2.2 (8.4)	0	0	0	0	0.904
Insomnia	71.1 (16.9)	54.4 (16.4)	49.4 (17)	66.7 (66.7–66.7)	66.7 (33.3–66.7)	66.7 (33.3–66.7)	0.003
Appetite loss	52.2 (20.9)	45.5 (18.6)	44.4 (16)	66.7 (33.3–66.7)	33.3 (33.3–66.7)	33.3 (33.3–66.7)	0.496
Constipation	11.1 (16)	26.6 (22.1)	19.7 (21.2)	0 (0–33.3)	33.3 (0–33.3)	33.3 (0–33.3)	0.034
Diarrhea	0	8.9 (14.9)	9.9 (15.4)	0	0 (0–25)	0 (0–33.3)	0.073
Financial difficulty	94.4 (15.5)	100	100	100	100	100	0.535

Table 5: Descriptive analysis of quality of life questionnaire-H&N35 symptom scales over time

Domain	Pre	Post	FF	Pre	Post	FF	p-value
Pain	72.5 (12.8)	56.1 (15.9)	38.3 (14.5)	75 (66.7–83.3)	50 (50–64.6)	33.3 (29.1–45.8)	0.000
Swallowing	70.3 (12.5)	59.4 (12.9)	50.3 (9.1)	70.8 (60.4–83.3)	58.3 (50–66.7)	50 (41.7–58.3)	0.000
Sense problem	46.7 (14.4)	44.9 (14)	37 (16.2)	41.6 (33.3–50)	41.6 (33.3–50)	33.3 (33.3–50)	0.176
Speech problem	60 (11.9)	59.3 (9.4)	53.9 (9.1)	61.1 (55.6–66.7)	55.6 (55.6–66.7)	55.6 (44.4–55.6)	0.176
Social eating	58.9 (10)	56.7 (8.6)	51.5 (8)	58.3 (50–66.7)	58.3 (50–58.3)	50 (50–58.3)	0.009
Social contact difficulty	61.2 (9.6)	54 (7.7)	46.7 (7.2)	60 (53.3–66.7)	53.3 (46.7–60)	46.7 (40–53.3)	0.000
Sexual interest	63.9 (11.6)	56.1 (11.2)	51.2 (12.2)	66.7 (54.2–66.7)	50 (50–66.7)	50 (50–66.7)	0.025
Teeth	64.4 (24.7)	58.9 (16.8)	50.6 (17)	66.7 (33.3–66.7)	66.7 (41.6–66.7)	66.7 (33.3–66.7)	0.118
Opening mouth	71.1 (19)	51.1 (19)	38.2 (22.1)	66.7 (66.7–66.7)	50 (33.3–66.7)	33.3 (33.3–33.3)	0.000
Dry mouth	0	26.6 (22.1)	44.4 (18.5)	0	33.3 (0–33.3)	33.3 (33.3–66.7)	0.000
Sticky saliva	2.2 (8.4)	25.5 (20.9)	48.1 (26.7)	0	33.3 (0–33.3)	66.7 (33.3–66.7)	0.000
Coughing	32.2 (16.3)	26.7 (25.4)	23.4 (22.3)	33.3 (33.3–33.3)	33.3 (0–33.3)	33.3 (0–33.3)	0.664

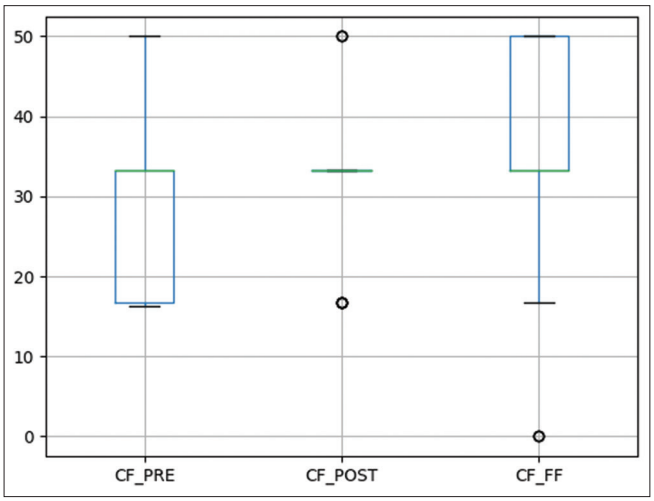

Fig. 5: Box plot showing variations in cognitive functioning score over the course of the study

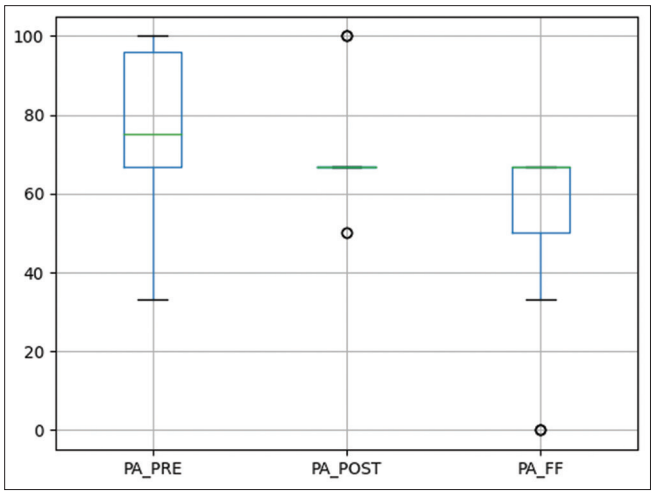

Fig. 6: Box plot showing variations in pain score over the course of the study

radiotherapy treatment in a palliative setting is resource-intensive and is not a feasible option in India where machine time and financial constraints are the major limiting factors [6,7].

Various palliative regimens have been tried in head-and-neck cancers like 30 Gy in 20 Fractions, 20 Gy in 5 Fractions, quad shot regimen and the christie regimen. In our study, all the patients were planned for 50 Gy in 20 fractions. The biological effective dose of this regimen is 62.5Gy, which is very close to the radical dose of 79.2Gy. Most of the palliative radiotherapy regimens in the head and neck are extrapolated from the palliative regimens used in other sites such as brain/bone metastasis. Tumor biology of head-and-neck squamous cell carcinomas are different and the use of a higher dose as used in our study is required for sustained palliation of symptoms. Very few studies have used such a high dose; Minatel *et al.* studied 58 patients who received 50 Gy in 20 fractions. The study used concurrent bleomycin and the delivery of radiotherapy was split into a course of two treatment sessions. Each course consisted of 25 Gy in 10 fractions for 2-week duration followed by a similar second course with a 2 weeks gap. The total duration of treatment was 6 weeks whereas in this study, it was 4 weeks [8-12].

Global health status score, functional scales score, and symptom scales score of EORTC QLQ 30 and H&N35 before radiotherapy, post radiotherapy, and 6 weeks after radiotherapy were analyzed using Mean (standard deviation) and Median (IQR) statistics and the Statistical significance was tested using the Non-parametric test for the related samples (Friedman's test). All of the functional scales were found significant in this study with PF, EF, and CF being significant at 1% alpha level while RF and SF are significant at 5% alpha level. RF was assessed based on the capabilities of the patient to finish daily activities. The median score remained at 33 but the IQR was showing an increasing trend [13,14].

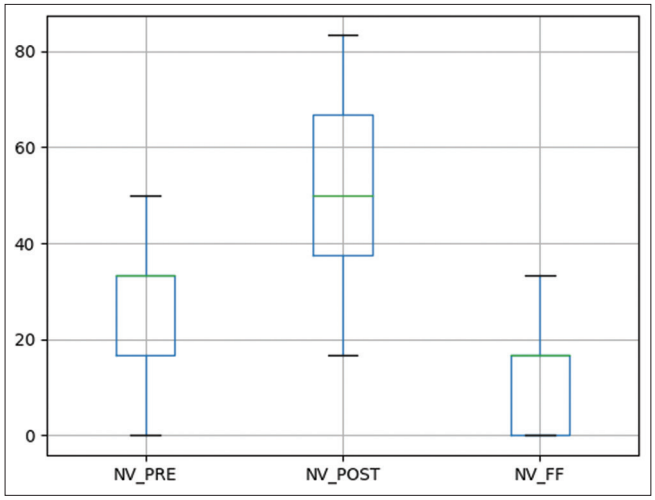

Fig. 7: Box plot showing variations in nausea and vomiting over the course of the study

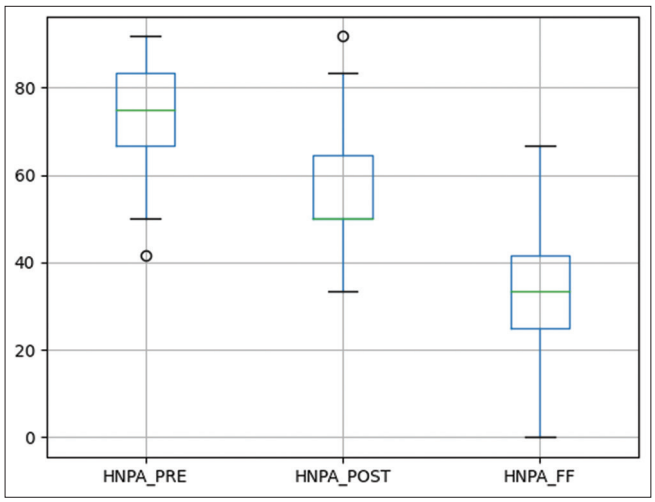

Fig. 8: Box plot showing variations in head and neck pain score over the course of the study

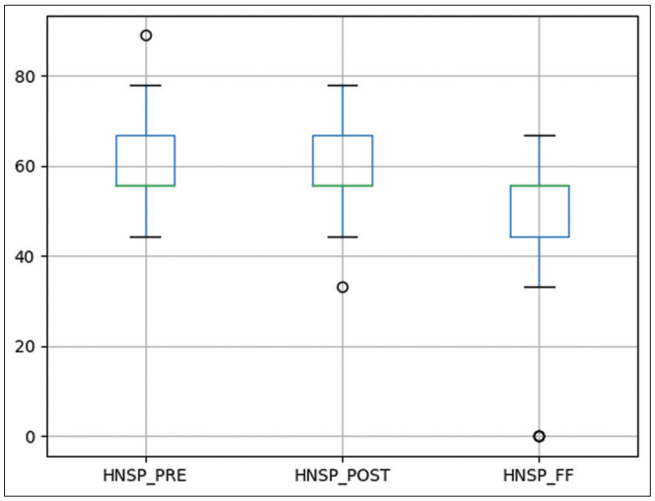

Fig. 9: Box plot showing variations in HNSP score over the course of the study

The goal of any palliative radiotherapy regimen is pain control and in our study both pain and head-and-neck-specific pain had significantly reduced over time. Fatigue had shown a constant reduction during radiation and during the first follow-up as well. The increase in nausea, vomiting, and constipation during radiation can be attributed to the use of morphine during radiation for pain control and as an effect of radiation itself. Our results were comparable to a Swedish study that analyzed 47 head-and-neck cancer patients of which 12 were oral cavity cancers [15]. They assessed the QoL at baseline, completion of radiotherapy, and at follow-up during 3, 6, and 12 months using the questionnaire EORTC QLQ-C30-version and HandN35. In this study, most of the functions showed a decreasing trend during radiation and returned to baseline within a year. Similar to our study, dry mouth was a late problem that affected the QoL during follow-up visits (Figs. 6 and 7).

The results on the improvement of nutritional status also showed a similar trend in both studies. There was weight loss during radiation which improved during subsequent follow-up visits [15-17] (Figs. 8 and 9).

In patients diagnosed with inoperable oral cavity cancer, hypofractionated radiotherapy delivering 50 Gy in 20 fractions over 4 weeks is a well-tolerated and safe regimen. In our study, statistically significant QoL improvement in global health score, SF, and CF lasting for a minimum of 6 weeks was attained after completion of treatment with this regimen. Based on the results of this study, a continuation of this study with a large sample size is needed. A randomized study using this radiotherapy regime in one arm versus conventional radiotherapy fractionation will be ideal to show the usefulness of this regime. Designing an Indian population-based QoL score addressing the cultural and ethnic practices of our country will be useful while conducting such studies in the future. Identifying a subgroup that will benefit from palliative radiotherapy is of utmost importance. Studies for the identification of a biomarker that will predict the response to palliative radiotherapy are still not conclusive [18].

Limitations

The follow-up duration was short. Studies with larger sample sizes would yield more convincing outcomes.

CONCLUSION

Palliative radiotherapy using 2.5Gy per fraction achieved reasonable palliation with good symptom control and an acceptable toxicity profile. In patients with inoperable oral cavity cancer, hypofractionated radiotherapy delivering 50 Gy in 20 fractions over 4 weeks is an effective, well tolerated, and safe regimen. Statistically significant QoL improvements lasting for a minimum of 6 weeks were obtained after completion of treatment with this regimen.

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