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Effectiveness of Structured Exercise Intervention in Cancer-Related Fatigue among Oral Cavity Cancer Patients: Randomized Controlled Trial

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Abstract

Introduction In head and neck cancer (HNC) patients, fatigue is present throughout the course of treatment and during follow-up. Cancer-related fatigue (CRF) is a significant treatment-related side effect experienced by oral cancer patients during and after treatment. CRF, when coupled with other side effects of oral cavity cancer, patients who undergo definitive treatment have some of the most dramatic acute side effects, and reduced overall quality of life (QoL). Although there are upcoming intervention strategies to manage CRF, the effect of exercise intervention is explored in this study. The rationale for considering exercise to manage CRF is that it may alleviate the combined effect of toxic treatment and decreased levels of activity during the treatment that reduces the capacity for physical performance.

Objective This study was conducted to investigate the effectiveness of exercise intervention on CRF, and its influence on functional capacity and QoL among patients with oral cavity cancer during and after their primary cancer treatment.

Materials and Methods Oral cavity cancer patients ($n = 223$), planned for only chemoradiotherapy with curative intent were screened for CRF. Based on the inclusion criteria, 69 patients were grouped randomly into experimental ($n = 35$) and control ($n = 34$) groups. Patients in the experimental group were provided structured exercise intervention, while the control group was offered standard and routine care. Structured exercise in this present study comprised moderate-intensity walking and resistance exercises using TheraBand every day for three to five times a week. CRF was assessed using symbolic assessment of fatigue extent and the functional capacity was assessed by 6-minute walk test (6MWT), maximal oxygen uptake (VO_{2max}), and hand dynamometer. QoL was assessed using the European Organization for Research and Treatment for Cancer-QoL (EORTC QLQ-C30) and the Head and Neck

Keywords
- cancer rehabilitation
- cancer-related fatigue
- exercise intervention
- functional capacity
- oral cavity cancer
- quality of life

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Cancer module (HN35), while distress was assessed by the National Comprehensive Cancer Network (NCCN) Distress Thermometer. Randomized patients were assessed at four points.

Result The size effects in fatigue extent ($\eta_p^2 = 0.40$) and fatigue impact ($\eta_p^2 = 0.41$) were found to be moderate, and a positive correlation between 6MWT, fatigue extent, and fatigue impact was observed.

Conclusion This study suggests that exercise intervention has a significant positive impact on CRF, most aspects of QoL, and the functional capacity of the patients.

Introduction

Oral cancer is the second most common cancer in India, accounting for 10.3% of the newly diagnosed cases in 2020.[1] In head and neck cancer (HNC) patients, fatigue is reported throughout the course of treatment and during follow-up.[2] Cancer-related fatigue (CRF) is a significant treatment-related side effect experienced by oral cancer patients during and after treatment. Patients frequently report CRF during and after chemotherapy or radiotherapy, the degree of which varies with the type of cancer.[3] As defined by the National Comprehensive Cancer Network (NCCN), CRF is a "distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning."[4] In contrast to fatigue of daily life, weariness, or exhaustion from labor, exertion, or stress, which are usually relieved by rest, CRF is related to the disease prognosis or its treatments and will not be alleviated by rest.[5] CRF also affects cancer treatment. It may compromise the timing or completion of treatment regimens, either because fatigue has a dose-limiting adverse effect or because it reduces the patient's willingness to adhere to the treatment regimen.[6] Prevalence studies with sample sizes above 1,000 reported CRF ranging from 14 to 66%[7] and a prospective Indian study on CRF among mixed cancer patients (45.6% HNC) reported that 84.5% had mild to moderate CRF and 3.3% had severe CRF.[8] A significant number of patients report CRF at the time of diagnosis and this number increases over the course of the treatment and lasts up to 3 to 4 weeks posttreatment. Concurrent treatment increases risk of developing or aggravating CRF.[3,8] HNC patients who undergo definitive treatment have some of the most dramatic acute side effects, which include, but are not limited to, severe mucositis, epidermal ulceration/desquamation of the neck, xerostomia, ageusia, and odynophagia, and when CRF is coupled with other side effects, it can be debilitating and lead to improper self-care, distress, malnutrition, loss of weight, productivity, and reduced overall quality of life (QoL).[9,10]

The NCCN-developed treatment guidelines for CRF recommend a moderate exercise training program to improve functional capacity and activity tolerance.[4] Many exercise programs for CRF are confined to 10 to 12 weeks of either aerobic or nonaerobic exercises.[11,12] However, the combination of home-based aerobic (walking) and anaerobic (resistance/therapeutic bands) exercises for cancer patients undergoing treatment is considered safe and executable, with greater adherence and positive influence on CRF and QoL.[13] The majority of the studies on exercise as an intervention on CRF were conducted among breast and prostate cancer patients, and few studies focused on other sites.[7] Clearly, knowledge of a patient's CRF status before treatment onset and, ideally, during treatment is critical for an accurate understanding of posttreatment CRF. Hence, this study aimed to establish the effectiveness of exercise as an intervention on CRF among oral cavity cancer during their cancer therapy.

Objective

The objective of the study was to investigate the effectiveness of exercise intervention on CRF, and its influence on functional capacity and QoL among patients with oral cavity cancer during and after their primary cancer treatment.

Materials and Methods

Design, Setting, and Participants

This study adopted a randomized controlled trial comparing structured exercise intervention with standard cancer care. The approval for the project was submitted to the Cancer Institute Ethical Committee. This study followed the principles of the Declaration of Helsinki and was approved by the ethical committee meeting dated February 13, 2013. The study was conducted at the Regional Cancer Centre Chennai on histopathologically confirmed oral cavity cancer patients registered between June 2015 and November 2016. The HNC patients registered during the study period were enlisted. Among the HNC patients, those indexed having oral cavity cancer were chosen. The selected patients were screened for CRF using the symbolic assessment of fatigue extent (SAFE).[14] Severe CRF patients were not included in the study. Patients aged between 18 and 65 years, between stages I and IVA, planned for chemoradiotherapy (CRT) with curative intent as per the decision of the multidisciplinary tumor board, and with a performance status between 0 and 2 based on the Eastern Cooperative Oncology Group (ECOG) were considered eligible for the study. Only patients with mild and moderate CRF were selected purposively for the main study for random assignment into control and experimental

groups for a structured exercise intervention. Patients with secondary cancer, severe CRF, and any physical comorbidity that would impair aerobic capacity or the ability to engage in physical activity, including diseases of the cardiovascular, pulmonary, neurological, metabolic, or musculoskeletal systems, and with nutritional deficiency (serum albumin <3.0 g/dL), or anemia (Hb <10 g) were excluded from the study. The medical records were used to screen the patients for the comorbidities, and the treating oncologists were also consulted for their fitness to take part in the study.

All the patients meeting the inclusion criteria were approached in the outpatient department and briefed about the study. Informed written consent was obtained from the patients to screen for CRF and to access their medical records and, if chosen, to participate in the structured exercise intervention. Following the screening, patients were randomized to prevent selection bias, and computer-generated random numbers were used for simple randomization of patients into control and experimental groups, with the help of a statistician. While the patients in the experimental group were provided structured exercise intervention, the control group was offered standard and routine cancer care.

Structured Exercise Intervention

The structured exercise intervention in this study focused on flexibility, muscle strength, and endurance, with an emphasis on strengthening proximal muscle groups and improving functional ability. All structured exercises were reviewed by the cancer rehab core team and followed the American College of Sports Medicine's (2000) general guidelines for exercise testing and prescription. The structured exercise in this study comprised moderate-intensity walking and resistance exercises using TheraBand.

Moderate-intensity walking (aerobic): Patients were advised to walk at their own pace for 20 minutes with mandatory 2 minutes of warm up with alternating cool down, three to five times in a week.

Minimal to moderate resistance exercise with TheraBand, grade 2 (anaerobic): Resistance exercise using TheraBand (grade 2) was structured based on prudent exercise guidelines. This comprised five sets of exercise that were structured for major muscle group of the upper limb: lateral raise, dynamic hug, chest press, reverse flies, and lateral pulldown.

The intensity of the structured exercise is guided by the Borg exertion scale for rating of perceived exertion (11–13/20 RPE). In the present study, patients were advised to do any three sets of exercise for 15 to 20 minutes in a day three to five times in a week. TheraBand (grade 2) and handout on exercise protocol and exercise adherence calendar were provided to the patients and the exercise was demonstrated to individual patients based on the protocol developed. The adherence to exercise was validated by the ward nurse during hospitalization and caregivers at home, using an adherence chart, and by the researcher over telephone, twice a week.

All the patients enrolled in the two groups were assessed at four points: before starting cancer treatment (assessment 1), between 14 and 21 days after commencement of CRT (assessment 2), completion of cancer treatment (assessment 3), and 3 months from completion of treatment (assessment 4). After the final assessment, the patients in the control group were sensitized about the proposed positivity of exercise in reducing CRF and improving functional capacity.

Primary outcome: CRF was assessed using the SAFE,[14] which contains 12 items measuring the extent and impact of CRF.

Secondary outcome: Functional capacity was assessed by the 6-minute walk test (6MWT), Burr's equation was used for maximal oxygen uptake (VO_{2max}), and grip strength was measured by the hand dynamometer. QoL was assessed using European Organization for Research and Treatment for Cancer- Quality of Life (EORTC QLQ-C30) and Head and Neck Cancer module (HN35), while distress was assessed using the NCCN Distress Thermometer.

Data Analysis

The data were analyzed using Statistical Package for the Social Sciences (SPSS) version 22.0. Age, gender, education, occupation, sociodemographic status, marital status, diagnosis, comorbidities, and treatment schedule were summarized using the frequency and proportions. The chi-squared test and independent *t*-test were used to assess the homogeneity of variance between experimental and control groups. Pearson's correlation analysis was used to find the relationship of CRF with distress, functional capacity, and QoL. Two-factor repeated measures analysis of variance was done to understand the interaction between two factors, namely, the assessment points (four points) and the condition, that is, the experimental and control groups, on the dependent variables. Pairwise comparisons were done separately for the experimental and control groups to understand the differences between the assessment points. Bonferroni correction was used to reduce the chances of obtaining false-positive results (type I errors), as multiple pairwise tests were performed on a single dependent variable. Sphericity, the variances of the differences between all combinations of related groups, was tested using Mauchly's test of sphericity. The Greenhouse–Geisser correction was used wherever Mauchly's test of sphericity was violated.

Results

The study participants' CONSORT (Consolidated Standards of Reporting Trials) flowchart is presented in ►**Fig. 1**. Of 223 oral cavity cancer patients screened for CRF, based on the inclusion criteria, 69 patients were included in the study and were randomized into the experimental ($n=35$) and control ($n=34$) groups. Of the 25 patients excluded, 14 were excluded due to severe CRF ($n=1$), comorbidities ($n=10$), physical disabilities ($n=2$), and mortality ($n=1$), while 11 did not consent to participate. Patients with mild and moderate CRF (41.7%; $n=93$) were eligible for study recruitment. Patients reported no CRF (57.8%;n=129) and those with severe CRF(0.5%;n=1) were excluded from the study.

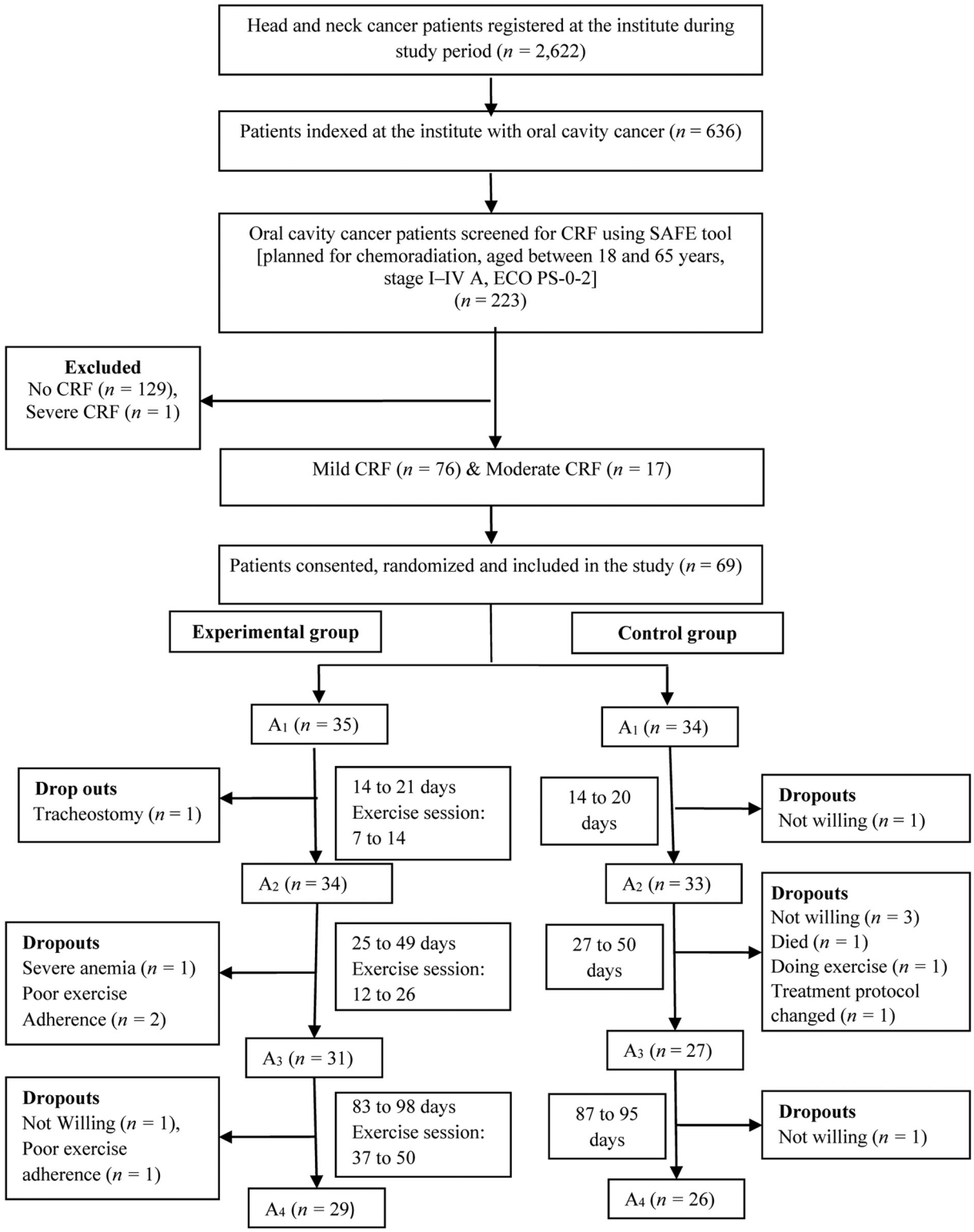

Fig. 1 CONSORT (Consolidated Standards of Reporting Trials) flowchart. A_1, baseline; A_2, between 14 and 21 days of chemoradiotherapy (CRT); A_3, on treatment completion; A_4, follow-up.

It is noted from the ►**Table 1** that the tongue and the cheek are the most commonly affected disease sites among the patients in both groups. With respect to the disease stage, a higher percentage of patients in both groups were in stage IVa. The baseline clinical characteristics and the CRT dose delivered were homogeneous, as noted in ►**Tables 1** and **2**, respectively.

The average duration between A_1 and A_4 was 139.34 days (131–153 days) in the experimental group and 148.04 (134–163 days) in the control group. The patients in the experimental group adhered to their exercise program for 73.48 (SD = 5.12) days. The majority of the patients (93%) adhered to the exercise schedule for 4 days per week. At the

Table 1 Demographic and clinical characteristics of oral cavity cancer patients in the experimental and control group ($N = 69$)

Variable	Categories	Total sample, *n* (%)	Experimental group, *n* (%)	Control group, *n* (%)	*p*-Value
Total		**69 (100)**	**35 (100)**	**34 (100)**	
Age (y)					
Mean (SD)		46.07 (9.23)	45.66 (8.15)	46.5 (10.32)	0.707[a]
Gender					
Male		57 (82.6)	29 (82.9)	28 (82.4)	0.956[b]
Female		12 (17.4)	6 (17.1)	6 (17.6)	
Marital status					
Married		65 (94.2)	34 (97.1)	31 (91.2)	0.520[b]
Single		4 (5.8)	1 (2.9)	3 (8.8)	
Education					
Primary		25 (36.2)	12 (34.3)	13 (38.2)	0.826[b]
Secondary		41 (59.4)	21 (60)	20 (58.8)	
Degree		3 (4.3)	2 (5.7)	1 (2.9)	
Disease site					
Floor of the mouth		3 (4.35)	1 (2.9)	2 (5.9)	0.830[b]
Tongue		36 (52.18)	19 (54.3)	17 (50)	
Cheek		21 (30.43)	12 (34.3)	9 (26.5)	
Retromolar trigone		2 (2.9)	1 (2.9)	1 (2.9)	
Gingiva		7 (10.1)	2 (5.7)	5 (14.7)	
Disease stage					
Stage II		1 (1.4)	–	1 (2.9)	0.262[b]
Stage III		16 (23.2)	6 (17.1)	10 (29.4)	
Stage Iva		52 (75.4)	29 (82.9)	23 (67.6)	
ECOG performance status					
Fully active (0)		55 (79.7)	26 (74.3)	29 (85.3)	0.256[b]
Restricted in physically strenuous activity (1)		14 (20.3)	9 (25.7)	5 (14.7)	

Abbreviations: ECOG, The Eastern Cooperative Oncology Group; *n*, frequency; SD, standard deviation.
[a]*t*-test.
[b]Chi–squared test.

Table 2 Completed treatment regimen of oral cavity cancer patients in experimental and control groups

Treatment regimen	Categories	Total sample, *n* (%)	Experimental group, *n* (%)	Control group, *n* (%)	*p*-Value
Total		**58 (100)**	**31 (100)**	**27 (100)**	
Concurrent CTx/RT					
Once every 3 week CDDP/66 Gy		32 (55.2)	15 (48.4)	17 (63.0)	0.398[a]
Weekly CDDP/66 Gy		21 (36.2)	13 (41.9)	8 (29.6)	
Weekly CDDP/60 Gy +10 Gy neck		2 (3.4)	2 (6.5)	–	
Once every 3 week CDDP/66 Gy		2 (3.4)	–	1 (3.7)	
Weekly carboplatin for 5-week/66 Gy		1 (1.7)	1 (3.2)	1 (3.7)	

Abbreviations: CDDP, cisplatin; CTx, chemotherapy; Gy, gray; RT, radiation therapy.
[a]Chi-squared value.

baseline, there were no significant differences in the fatigue extent and fatigue impact, distress, QoL, and functional capacity between the experimental and control groups.

Cancer-Related Fatigue

Fatigue extent and impact increased during the course of treatment and immediately after the completion of the treatment in both the groups as noted in ►**Table 3**. Statistically significant difference was noted immediately after the completion of treatment and during follow-up, but not during treatment. More than half of the patients in the experimental group had severe CRF during treatment (55.9%) and at completion of treatment (64.5%). A significant effect of exercise intervention on CRF among the patients at completion of treatment ($p < 0.05$) and at follow-up ($p < 0.01$) was reported. The size effect in both fatigue extent ($\eta_p{}^2 = 0.40$) and impact ($\eta_p{}^2 = 0.41$) was found to be moderate. Statistically, the interactional effect of four assessments and the two groups was significant in the extent of fatigue ($F = 11.30$; $p < 0.01$) and fatigue impact ($F = 12.14$; $p < 0.01$). The majority of the patients in the two groups experienced moderate level of CRF at baseline. In the experimental group, more than half of the patients had severe CRF during treatment (55.9%) and at completion of treatment (64.5%). But at follow-up, ~69% of the patients experienced moderate CRF and around one-fourth of them had severe CRF. In contrast, the majority of patients in the control group had severe CRF during treatment (90.9%), on completion of treatment (100%), and at follow-up (92.5%). About 69% of patients in the control group had severe impact of CRF during follow-up, whereas only 3.4% of patients in the experimental group had severe impact. ►**Table 4** indicates that experimental group experienced less severity of CRF compared with the control group.

Functional Capacity

A comparison between the two groups showed significant differences at A_2, A_3, andA_4 ($p < 0.01$). The patients in the experimental group covered better 6-minute walk distance (6MWD) than those in the control group after treatment completion and at follow-up. Effect size of intervention on 6MWD is found to be moderate ($\eta_p{}^2 = 0.22$). There is a significant interaction effect of four assessments and the two groups in the 6MWD ($F = 6.62$). In the experimental group, VO_{2max} decreased during the course of treatment and immediately after the completion of the treatment. It improved during follow-up, but the VO_{2max} of the control group remained the same during A_2, A_3, and A_4. The VO_{2max} of the experimental group was high compared with that of the control group A_2 (2.76^{**}), A_3 (2.50^{**}), and A_4 (2.86^{**}), and the difference was statistically significant. The interactional effect of four assessments and the two groups is significant in the VO_{2max} ($F = 4.36$). The effect size for VO_{2max} ($\eta_p{}^2 = 0.21$) indicated moderate effect size.

The mean value of the left-hand grip strength was 24.86 at A_2, 26.77 at A_3, and 27.1 at A_4 in the experimental group and 22.71 at A_2, 21.76 at A_3, and 23.24 at A_4 in the control group. No significant difference was observed in the values of the right- and left-hand grip strengths at A_4, between the two groups. The effect size of the right- and left-hand grip strengths between the two groups is found to be trivial and moderate, respectively.

Quality of Life

The mean global health status score of the experimental and control groups during the course of treatment was 51.71 and 48.99, respectively. At completion of treatment, it was 51.88 and 45.06, and at follow-up, it was 74.71 and 49.04, respectively, in the experimental and control groups. There was a significant difference between the two groups during treatment, at completion of treatment, and at follow-up in the physical functioning, role functioning, and cognitive functioning ($p < 0.01$). While the functional domains of the experimental group improved at follow-up from that of the baseline, the control group showed a decline compared with the baseline. Moderate effect size was observed in the global health status ($\eta_p{}^2 = 0.21$), physical functioning ($\eta_p{}^2 = 0.24$), role functioning ($\eta_p{}^2 = 0.21$), emotional functioning ($\eta_p{}^2 = 0.20$), and cognitive functioning ($\eta_p{}^2 = 0.22$) of the experimental group.

The interactional effect of assessments and the two groups is significant in symptoms of CRF ($F = 4.16$), pain ($F = 6.27$), dyspnoea ($F = 5.55$), insomnia ($F = 4.10$), appetite loss ($F = 6.68$), constipation ($F = 4.90$), and diarrhea ($F = 3.06$). Moderate effect size was observed in nausea ($\eta_p{}^2 = 0.24$), pain (0.21), constipation (0.21), diarrhea (0.25), and financial difficulties (0.21).

Irrespective of the group, the site-specific issues of HNCs worsened during treatment and at completion, while the same reduced at follow-up in the experimental group. There was a significant difference in the levels of pain, swallowing, speech, and social contact ($p < 0.01$) at baseline and at follow-up in the experimental group.

The two groups differed significantly in the levels of pain, swallowing, and mouth opening during the course of treatment, at completion of treatment, and at follow-up at ($p < 0.01$).

Distress

The mean distress score of the experimental and control groups was found to be 3.34 and 3.02, respectively. Although the mean distress score of the experimental group increased during the course of treatment and immediately after the completion of the treatment, the distress scores decreased during follow-up.

Interrelation of CRF, Distress, Functional Capacity, and QoL

A significant inverse relationship was found between the 6MWD and CRF extent and impact. While the CRF extent and impact were inversely related to the physical, role, and emotional functional domains of QoL, the VO_{2max} was positively related with the global health status ($r = 0.263$). Similarly, the right-hand grip strength was positively correlated to the physical functioning of QoL, as shown in ►**Table 5**.

Table 3 Comparison between four assessments and study groups, means, SDs, *t* values, and effect size for CRF, distress, functional capacity, and QoL of oral cavity cancer patients

Variable	Assessments								ANOVA interaction (*F*-Value)	Partial eta squared
	A_1		A_2		A_3		A_4			
	M (SD)	*t*-Value	M (SD)	*t*-Value	M (SD)	*t*-Value	M (SD)	*t*-Value		
Fatigue extent[a]										
Experimental	3.77[(b)(c)(d)] (1.21)	0.51[NS]	5.62 (2.00)	0.71[NS]	6.52[(d)] (2.12)	2.11[b]	4.72 (1.33)	3.10[c]	11.30[c,d]	0.40
Control	3.82[(b)(c)(d)] (1.11)		7.70[(c)(d)] (1.92)		9.30 (1.29)		7.58 (2.02)			
Fatigue impact[a]										
Experimental	7.77 (4.22)	0.24[NS]	9.35[(c)(d)] (3.97)	0.52[NS]	9.71 (2.75)	2.53[b]	7.24 (2.81)	3.75[c]	12.14[c,d]	0.41
Control	8.35[(b)(c)] (3.44)		12.70 (3.08)		14.37 (3.39)		13.80 (2.82)			
Distress[a]										
Experimental	3.34[(c)] (1.21)	0.16[NS]	3.76[(c)] (1.10)	0.29[NS]	4.09 (1.16)	0.69[NS]	3.03 (0.73)	0.05[NS]	0.62[NS]	0.19
Control	3.02[(b)(c)(d)] (1.05)		3.66 (1.16)		4.81 (1.30)		3.65 (1.26)			
Functional capacity: 6-min walk distance (m)										
Experimental	448.03[(c)] (74.51)	0.61[NS]	425.00 (88.40)	2.80[c]	418.68[(d)] (71.97)	2.72[c]	448.72 (59.06)	2.86[c]	6.62[b,d]	0.22
Control	444.97[(b)(c)(d)] (94.66)		374.36 (84.24)		351.48 (64.44)		335.00 (60.34)			
VO_2 max										
Experimental	48.94[(b)(c)(d)] (4.10)	0.13[NS]	40.13 (4.34)	2.76[c]	39.84 (4.49)	2.50[b]	41.93 (3.62)	2.86[c]	4.36[b,d]	0.21
Control	47.03[(b)(c)(d)] (4.88)		37.09 (4.50)		37.37 (4.79)		37.50 (5.03)			
Hand grip, right										
Experimental	28.29 (12.93)	0.63[NS]	26.76 (12.01)	2.23[b]	26.61 (12.50)	2.20[b]	26.72 (11.49)	1.20[NS]	1.95[NS]	0.24
Control	26.28[(b)(c)(d)] (10.81)		23.07 (7.91)		22.92 (8.04)		23.49 (7.90)			
Hand grip, left										
Experimental	27.51 (13.00)	0.33[NS]	24.86 (12.65)	2.10[b]	26.77 (11.79)	2.43[b]	27.18 (11.25)	1.25[NS]	2.70[NS]	0.18
Control	25.66[(c)] (11.24)		22.71 (8.58)		21.76 (9.35)		23.24 (8.57)			
EORTC QoL: global health status										
Experimental	58.81[(d)] (19.69)	0.37[NS]	51.71[(c)(d)] (14.61)	2.16[b]	51.88 (13.38)	1.99[b]	74.71 (10.32)	2.63[c]	6.66[c,d]	0.21
Control	55.88[(c)] (17.22)		48.99 (15.55)		45.06 (14.10)		49.04 (22.52)			
Physical functioning										
Experimental	87.81[(b)(c)] (16.12)	0.13[NS]	78.63 (20.48)	2.90[c]	72.90[(d)] (18.37)	2.14[b]	83.91 (16.38)	2.01[b]	3.67[b,d]	0.24
Control	82.75[(c)] (19.77)		76.36 (19.44)		66.42 (25.65)		60.26 (27.48)			

(*Continued*)

Table 3 (*Continued*)

Variable	Assessments								ANOVA interaction (*F*-Value)	Partial eta squared
	A_1		A_2		A_3		A_4			
	M (SD)	*t*-Value	M (SD)	*t*-Value	M (SD)	*t*-Value	M (SD)	*t*-Value		
Role functioning										
Experimental	86.67[(b)(c)(d)] (22.43)	0.86[NS]	81.86 (20.25)	2.37[b]	64.52 (18.63)	2.02[b]	86.78 (15.67)	2.86[c]	4.90[b,d]	0.21
Control	84.80[(c)] (21.06)		77.27 (24.58)		70.37 (22.80)		66.03 (21.84)			
Emotional functioning										
Experimental	79.52 (18.56)	0.00[NS]	78.92 (14.82)	0.50[NS]	77.42 (13.64)	0.20[NS]	83.91 (10.89)	0.01[NS]	2.20[NS]	0.20
Control	87.25[(c)(d)] (10.10)		75.25 (20.14)		73.46 (16.99)		66.35 (21.14)			
Cognitive functioning										
Experimental	91.90[(c)(d)] (14.7)	0.68[NS]	86.27 (19.45)	2.91[c]	77.96 (17.94)	2.46[b]	94.25 (12.81)	2.90[c]	7.37[c,d]	0.22
Control	91.18[(c)] (15.48)		81.31 (21.55)		82.10 (16.61)		73.72 (21.17)			
Social functioning										
Experimental	70.48 (30.27)	0.42[NS]	71.08 (20.23)	0.19[NS]	74.73 (19.18)	0.54[NS]	81.61 (18.00)	0.04[NS]	2.33[NS]	0.24
Control	70.10 (34.02)		69.19 (26.06)		77.16[(d)] (20.22)		63.46 (23.57)			
Fatigue[a]										
Experimental	29.84 (20.12)	0.51[NS]	31.37 (18.64)	2.59[c]	41.22[(d)] (15.23)	2.00[b]	27.59 (23.68)	3.10[c]	4.16[b,d]	0.17
Control	26.80[(d)] (17.75)		30.30 (18.48)		41.98 (27.96)		50.43 (24.99)			
Nausea vomiting[a]										
Experimental	12.38[(c)] (16.83)	0.55[NS]	17.16 (13.90)	0.95[NS]	27.96 (16.32)	0.21[NS]	18.97 (18.75)	0.11[NS]	2.44[NS]	0.24
Control	12.75[(c)(d)] (19.27)		20.71 (16.68)		29.63 (22.32)		35.26 (25.09)			
Pain[a]										
Experimental	29.05 (22.63)	0.65[NS]	28.92 (20.23)	2.19[b]	32.80[(d)] (17.99)	2.07[b]	16.09 (12.18)	2.68 [c]	6.27[c,d]	0.21
Control	22.06[(d)] (23.10)		31.31 (25.26)		33.33 (26.55)		42.95 (26.32)			
Dyspnoea[a]										
Experimental	5.71[(c)] (17.12)	0.97[NS]	11.76 (10.13)	2.25[b]	19.35 (12.40)	2.96[c]	15.75 (12.81)	2.05[b]	5.55[c,d]	0.19
Control	5.88[(b)(c)] (15.28)		17.17 (22.23)		27.16 (24.52)		33.33 (28.28)			
Insomnia[a]										
Experimental	18.10 (30.6)	0.52[NS]	26.47 (15.66)	0.96[NS]	27.96[(d)] (19.43)	0.62[NS]	12.64 (8.71)	2.36[b]	4.10[b,d]	0.18
Control	22.55[(d)] (25.58)		28.28 (25.16)		39.51 (20.74)		42.31 (25.91)			

Table 3 (*Continued*)

Variable	Assessments								ANOVA interaction (*F*-Value)	Partial eta squared
	A_1		A_2		A_3		A_4			
	M (SD)	*t*-Value	M (SD)	*t*-Value	M (SD)	*t*-Value	M (SD)	*t*-Value		
Appetite loss[a]										
Experimental	25.71 (36.23)	0.01^{NS}	28.43 (16.12)	0.76^{NS}	31.18 (19.12)	0.00^{NS}	17.24 (12.12)	2.10^{b}	$3.68^{b,d}$	0.19
Control	$18.63^{(d)}$ (20.4)		23.23 (14.27)		38.27 (30.24)		50.00 (32.99)			
Constipation[a]										
Experimental	25.71 (36.23)	0.00^{NS}	20.59 (23.23)	0.54^{NS}	27.96 (19.43)	0.62^{NS}	16.09 (12.95)	2.06^{b}	$4.90^{b,d}$	0.21
Control	$13.73^{(d)}$ (23.38)		24.24 (20.87)		33.33 (22.64)		29.49 (18.79)			
Diarrhea[a]										
Experimental	7.62 (19.94)	0.36^{NS}	13.73 (8.56)	0.14^{NS}	12.90 (6.50)	0.01^{NS}	10.34 (5.69)	2.76^{b}	$3.06^{b,d}$	0.25
Control	$10.78^{(d)}$ (21.2)		22.22 (13.07)		24.69 (15.08)		37.18 (28.79)			
Financial difficulties[a]										
Experimental	37.41 (39.41)	0.42^{NS}	46.08 (31.79)	0.88^{NS}	44.09 (26.36)	0.25^{NS}	46.67 (40.68)	0.15^{NS}	0.91^{NS}	0.21
Control	42.16 (35.11)		37.37 (33.08)		33.33 (34.59)		39.74 (34.01)			
Pain[a]										
Experimental	$36.67^{(c)}$ (21.21)	0.10^{NS}	44.12 (19.41)	2.27^{b}	56.99 (19.84)	2.42^{b}	28.16 (18.15)	2.68^{c}	$8.50^{c,d}$	0.23
Control	$27.21(^{b)(c)(d)}$ (14.9)		42.17 (22.62)		53.40 (24.70)		55.13 (21.61)			
Swallowing[a]										
Experimental	$26.19^{(c)(d)}$ (25.73)	0.45^{NS}	37.75 (23.14)	2.54^{b}	50.00 (19.48)	2.32^{b}	18.97 (12.14)	2.18^{b}	$6.13^{c,d}$	0.20
Control	$19.61(^{b)(c)(d)}$ (21.08)		45.96 (26.69)		48.46 (23.57)		62.82 (77.50)			
Senses problem[a]										
Experimental	$25.24^{(c)}$ (26.92)	0.62^{NS}	33.33 (24.95)	0.92^{NS}	41.40 (17.67)	0.28^{NS}	30.46 (24.82)	0.99^{NS}	1.25^{NS}	0.22
Control	$21.08^{(c)}$ (29.95)		37.88 (23.67)		50.00 (25.31)		44.23 (26.22)			
Speech problem[a]										
Experimental	21.59 (21.03)	0.15^{NS}	$28.10^{(d)}$ (19.95)	0.70^{NS}	29.39 (16.86)	0.67^{NS}	14.18 (11.07)	0.00^{NS}	$5.88^{c,d}$	0.21
Control	$13.07^{(b)(c)}$ (16.5)		28.62 (22.40)		34.16 (16.85)		32.05 (22.07)			
Trouble with social eating[a]										
Experimental	23.10 (26.43)	0.21^{NS}	$31.62^{(d)}$ (20.39)	0.75^{NS}	33.87 (17.99)	0.01^{NS}	19.25 (12.22)	0.06^{NS}	$5.16^{c,d}$	0.18
Control	$14.71^{(b)(c)}$ (14.8)		31.82 (21.19)		37.35 (24.28)		37.50 (23.12)			

(*Continued*)

Table 3 (*Continued*)

Variable	Assessments								ANOVA interaction (*F*-Value)	Partial eta squared
	A_1		A_2		A_3		A_4			
	M (SD)	*t*-Value	M (SD)	*t*-Value	M (SD)	*t*-Value	M (SD)	*t*-Value		
Trouble with social contact[a]										
Experimental	19.05$^{(c)}$ (22.76)	0.10^{NS}	24.31 (19.75)	0.42^{NS}	31.18 (18.65)	0.28^{NS}	14.25 (10.03)	0.00^{NS}	6.9^{c,d}	0.21
Control	10.78$^{(b)(c)}$ (15.13)		28.89 (21.58)		32.35 (20.14)		38.97 (23.14)			
Teeth[a]										
Experimental	14.29$^{(c)}$ (23.27)	0.19^{NS}	31.37 (29.52)	0.53^{NS}	47.31 (33.08)	0.22^{NS}	24.14 (30.72)	0.40^{NS}	1.52^{NS}	0.22
Control	23.53$^{(b)}$ (29.0)		35.35 (27.56)		46.91 (28.13)		44.87 (32.58)			
Opening mouth[a]										
Experimental	49.52$^{(c)}$ (31.6)	0.38^{NS}	50.00 (28.72)	2.13^{b}	69.89 (21.69)	2.43^{b}	55.17 (28.55)	2.72^{c}	5.10^{c,d}	0.18
Control	36.27$^{(d)}$ (30.0)		52.53 (35.38)		56.79 (30.40)		75.64 (24.14)			
Dry mouth[a]										
Experimental	25.71$^{(c)}$ (33.41)	0.01^{NS}	44.12 (26.86)	0.09^{NS}	48.39 (20.79)	0.49^{NS}	37.93 (21.31)	0.00^{NS}	4.91^{c,d}	0.18
Control	13.73($^{(b)(c)(d)}$ (21.89)		47.47 (33.36)		58.02 (25.47)		57.69 (30.63)			
Sticky saliva[a]										
Experimental	28.57$^{(c)}$ (35.37)	0.27^{NS}	39.22 (23.88)	0.74^{NS}	50.54 (24.14)	0.45^{NS}	32.18 (24.36)	0.01^{NS}	1.56^{NS}	0.22
Control	22.55$^{(b)(d)}$(28.09)		45.45 (28.64)		53.09 (21.20)		47.44 (31.51)			
Coughing[a]										
Experimental	22.86 (25.27)	0.59^{NS}	27.45 (25.25)	0.50^{NS}	25.81 (26.81)	0.69^{NS}	13.79 (24.42)	0.04^{NS}	2.50^{NS}	0.24
Control	18.63$^{(b)}$ (23.48)		37.37 (29.76)		33.33 (29.23)		33.33 (33.99)			
Felt ill[a]										
Experimental	20.95$^{(c)}$ (24.3)	0.17^{NS}	33.33 (27.21)	2.55^{b}	47.31 (28.25)	2.71^{c}	32.18 (10.84)	0.00^{NS}	1.20^{NS}	0.23
Control	11.76$^{(c)(d)}$ (18.13)		30.30 (26.82)		45.68 (30.86)		44.87 (26.57)			

Note: Superscripts with the mean values indicate multiple comparisons between the assessment using Bonferroni corrections.
Abbreviations: A_1(a), baseline; A_2(b), between 14 and 21 days of chemoradiotherapy (CRT); A_3(c), on completion of treatment; A_4(d), 3 months of follow-up. M, Mean. NS, Not significant. SD, Standard deviation.
[a]Lower scores are beneficial.
[b]$p < 0.05$.
[c]$p < 0.01$.
[d]Statistically significant after Bonferroni correction.

Table 4 Percentage distribution of severity of cancer-related fatigue (CRF) among oral cavity cancer patients of experimental and control group during the four assessments

CRF	Experimental, *n* (%)				Control, *n* (%)			
	A_1 ($n=35$)	A_2 ($n=34$)	A_3 ($n=31$)	A_4 ($n=29$)	A_1 ($n=34$)	A_2 ($n=33$)	A_3 ($n=27$)	A_4 ($n=26$)
Fatigue extent								
Mild	7 (20.0)	1 (2.9)	–	1 (3.4)	6 (17.6)	1 (3.0)	–	–
Moderate	28 (80.0)	14 (41.2)	11 (35.5)	20 (69.0)	28 (82.4)	2 (6.1)	–	2 (7.7)
Severe		19 (55.9)	20 (64.5)	8 (27.6)		30 (90.9)	27 (100)	24 (92.3)
Fatigue impact								
Mild	11 (31.4)	6 (17.6)	2 (6.5)	7 (21.4)	8 (23.5)	–	1 (3.7)	–
Moderate	16 (45.7)	24 (70.6)	24 (77.4)	21 (72.4)	20 (58.8)	15 (45.5)	5 (18.5)	8 (30.8)
Severe	8 (22.9)	4 (11.8)	5 (16.1)	1 (3.4)	6 (17.6)	18 (54.5)	21 (77.8)	18 (69.2)

Abbreviations: A_1, baseline before starting cancer treatment; A_2, assessments between 14 and 21days; A_3, on completion of cancer treatment; A_4, 3 months of follow-up.

Discussion

The findings of the present study show that a structured exercise intervention was effective in mitigating CRF in its extent and impact, while also improving the QoL and functional capacity of oral cavity cancer patients. The experimental group in the present study recorded a decrease in the extent of CRF and its impact experienced during and at follow-up treatment. These findings are in line with the existing global literature emphasizing the constructive effect of long-term exercise intervention on CRF.[15–19] Similar findings have been reported in studies from an Indian context, stating significant reduction in CRF post 6 weeks of aerobic exercise intervention[20] and that patients with no exercise report intensification of CRF symptoms as compared with the experimental group.[19,21–23] These findings could be attributed to the fact that exercise mitigates CRF and may alleviate the combined effects of toxic treatment and decreased levels of activity during treatment that reduce the capacity for physical performance. The literature emphasizes improved QoL, optimistic feelings, and reduced CRF in exercise intervention.[19,20,23,24]

The duration and frequency of exercises reported in the present study to understand the long-term effects of exercise therapy were analogous to the exercise schedules described in the studies included in a meta-analysis.[3] The effect size for extent of fatigue ($\eta_p{}^2 = 0.40$) and its impact ($\eta_p{}^2 = 0.41$) was found to be moderate in this study. This is in line with the findings of the earlier studies which indicated that a clinically pertinent impact on alleviation of CRF symptoms after exercise intervention with the effect size of ($\eta_p{}^2 = 0.44$) and effect size being ($\eta_p{}^2 = 0.33$), respectively.[17,25]

The present study reported no significant difference in the right- and left-hand grips, despite the higher mean values in the experimental group. This finding is in contrast with the study reporting a significant increase in the handgrip within and between two groups of breast cancer survivors, with one group receiving yoga with aerobic exercise and the other receiving aerobic exercise alone.[26]

The results of this study indicate an increase in the mean values of the VO_{2max} between the experimental and control groups at the end of the study. Many studies have demonstrated that structured exercise intervention during therapy, on completion of treatment, and in the follow-up period significantly increased the VO_{2max} in oral cavity cancer patients.[16,27,28] The results of earlier research helped infer that the VO_{2max} of cancer patients improved as a result of any type of exercise training regardless of the nature of treatment, although the effect size may vary with different forms of exercise.[29–31]

The present study shows that patients in the experimental group covered significantly greater 6MWD during treatment. This is in line with the 8-minute single-stage walking test conducted among women treated for breast cancer stating a significantly increased aerobic fitness in the intervention group including both exercise and exercise-placebo groups than in the control group after 8 weeks.[32] 6MWT is a reliable tool and is significantly related to VO_{2max}, which is appropriate to be used among cancer patients.[33] The results of our study are in line with the studies done with a similar 5-week exercise program in myeloma patients during chemotherapy[34] and an Indian study done among HNC patients who underwent a 6-week exercise program.[35] Both studies found a significant decrease in the 6MWD in the control group. Researches on 6MWT, similar to our study, have reported globally that consistent exercise enhances the functional status in cancer patients.[20,23,35,36]

The results of the present study establishes a high functional status among patients and this is promising as the literature suggests functional status as a significant predictor of survival.[37] Previous studies have emphasized that exercise has a positive outcome on endurance and stamina by achieving better functional capacity and can thus bring in favorable changes in the health status of cancer patients.[22,32,38–41] Sprod et al also reported improved functional capacity with enhanced cardiovascular endurance and diminished fatigue and depression in breast cancer patients irrespective of the duration of training given.[42]

Table 5 Interrelation of cancer-related fatigue (CRF), distress, functional capacity, and QoL of oral cavity cancer patients at baseline ($N = 69$)

CRF		Distress	Functional capacity				EORTC quality of life					
CRF extent	CRF impact		Hand grip strength, right	Hand grip strength, left	6-min walk distance	VO_{2max}	Global health status	Physical function	Role function.	Emotional function	Cognitive function	Social functioning
1												
0.578[a]	1											
−0.093	0.008	1										
−0.229	−0.097	0.064	1									
−0.165	−0.024	0.090	0.962[a]	1								
−0.270[b]	−0.298[b]	−0.154	−0.156	−0.157	1							
0.191	0.136	−0.101	0.074	0.025	0.414[a]	1						
−0.164	−0.188	−0.370[a]	0.127	0.027	0.067	0.263[b]	1					
−0.346[a]	−0.345[a]	−0.130	0.293[b]	0.267[b]	0.169	0.171	0.369[a]	1				
−0.284[b]	−0.338[a]	0.091	0.164	0.125	−0.035	−0.018	0.149	0.347[a]	1			
−0.296[b]	−0.276[b]	0.063	−0.040	−0.017	−0.009	−0.165	0.104	0.262[b]	0.337[a]	1		
−0.213	−0.238[b]	0.023	0.190	0.207	−0.088	0.127	0.235	0.313[a]	0.039	0.309[a]	1	
−0.086	−0.223	0.207	0.067	0.037	0.118	0.124	0.134	0.264[b]	0.230	0.212	0.099	1

Abbreviation: EORTC, European Organization for Research and Treatment for Cancer.
Note: The values represent correlation coefficient "*r*."
[a]$p < 0.01$.
[b]$p < 0.05$.

Further, this study showed a significant decrease in the mean values of distress score in the experimental group, which is consistent with the results of other studies.[22,23] Comparable results of the association between designed exercise programs and improvement of QoL were found in this study and is supported by the literature.[30,32,35,43–45]

The strength of this study is that the patients who experienced CRF before their cancer treatment were chosen and examined the effect of structured exercise intervention during the course of treatment and at follow-up. This study is also unique in that it performed an extensive analysis on the correlation between CRF, distress, QoL, and functional capacity among oral cavity cancer patients. Results indicate a positive correlation between 6MWD, fatigue extent, and fatigue impact.

The present study suggests that structured exercise intervention has a significant positive influence on the impact and extent of CRF, most aspects of QoL, and on the functional capacity of the patients. This may be attributed to the fact that swallowing pathway and respiratory functions are usually affected in oral cavity cancer patients undergoing CRT. During the course of the treatment, this group of patients often depend on liquid diet or might even require nasogastric tube feeding as they develop oral mucositis. Oral mucositis is a major cause of pain and undernutrition in patients with oral cavity cancer. The exercise schedules add advantage by enhancing the functional status. The study also suggests that exercise is an efficient strategy in the management of CRF regardless of the type of treatment and in maintaining the status of physical activity.

Limitations and Implications of the Study

The small sample size limits the generalization of the study findings. Oral mucositis as a major cause of pain and undernutrition during CRT in patients with oral cavity cancer is not deeply explored.

The study found that a moderate-intensity structured exercise improves the functional capacity with concomitant reduction in CRF regardless of the time of treatment. Therefore, it can be made the standard of care in cancer rehabilitation. Although oral mucositis can cause significant pain and undernutrition during CRT in patients with oral cavity cancer, exercise sessions are feasible and improve the functional capacity and treatment completion.

Future research can focus on multicentric RCTs with long-term follow-ups, after home-based exercise intervention to mitigate CRF.

Conclusion

The present study observed a decrease in CRF with exercise in oral cavity cancer patients during and after concurrent CRT. Exercise also led to significant reduction in distress and significant improvement in health-related QoL and functional capacity in oral cavity cancer patients, as indicated by improved 6MWD, VO_{2max}, and hand grip.

Ethical Approval

The approval for the project was submitted to the Cancer Institute Ethical Committee. This study followed the principles of the Declaration of Helsinki and was approved by the ethical committee meeting dated February 13, 2013. The study was conducted at the Regional Cancer Centre, Chennai.

Conflict of Interest

None declared.

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