RESEARCH ARTICLE

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Effect of Structured Exercise-based rehabilitation on Sarcopenia and Quality of life among Head and Neck Cancer Patients Undergoing Chemo-radiotherapy: A Randomized Controlled Trial

Cherishma D'Silva[1]*, Vijith Shetty[2], Donald Fernandes[3], Baeyen Jean-Pierre[4], Sucheta Kumari[5], Saumya Srivastava[6], Stephen Rajan Samuel[7]

Abstract

Background: Sarcopenia is considered an independent prognostic factor for overall survival and performance status in head and neck cancer (HNC) receiving chemo-radiotherapy (CRT). CRT is known to cause sleep disturbances, increased pain perception, depression leading to reduced quality of life (QOL). Exercise-based rehabilitation has emerged as a promising strategy for improving outcomes in HNC. Our study aimed to evaluate effect of exercise on sarcopenia and QOL in patients with HNC receiving CRT. **Methodology:** Seventy HNC patients, aged 40-70 years TNM stage III- IVb receiving CRT, were randomized into two groups and received intervention for seven weeks. Intervention Group, IG (n=40) received combined aerobic and resistance training according to the ACSM guidelines. Control Group, CG (n=40) were advised to walk according to the NCCN guidelines. Sarcopenia was assessed using Bio Impedance Analyser (BIA), muscle strength using JAMAR hand dynamometer and QOL by FACT H&N on pre CRT day 1 and post 7 weeks. Wilcoxon signed-rank test and Mann-Whitney U test were used to assess within-group differences and between-group comparisons respectively. **Results:** 80 participants with a mean age of 58.44 ±3.75 years were included. IG showed a smaller decrease in total skeletal muscle mass compared to CG with IGs total skeletal muscle mass decreasing from 35 to 30 and CGs muscle mass decreasing from 40 to 21 ($p<0.001$). QOL showed significant improvement in CG from 66 to 61 ($p < 0.001$). In contrast, IGs quality of life saw a minor, non-significant change from 62 to 61. **Conclusion:** Sarcopenia was lesser in IG compared to CG, highlighting the favourable impact of resistance training and its inclusion in the HNC rehabilitation. However, CG demonstrated significant improvements in quality of life as compared to IG suggesting that quality of life is a multifaceted construct that may not be directly correlated with physical improvements alone.

Keywords: Head and Neck cancer- exercise-based rehabilitation- Sarcopenia- Quality of life

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Introduction

Head and neck cancers (HNC) represent a diverse group of malignancies that affect the oral cavity, pharynx, larynx, nasal cavity, and salivary glands. These cancers predominantly arise from squamous cells lining the mucosal surfaces of the head and neck. HNC is a global health concern, contributing significantly to the burden of cancer-related morbidity and mortality worldwide [1, 2]. According to International Head and Neck Cancer Epidemiology (INHANCE) consortium, head and neck cancers rank as the sixth most common cancers globally, accounting for more than 550,000 new cases each year and approximately 380,000 deaths [3].

Due to the location and aggressiveness of these tumors, patients often face challenges related to breathing, swallowing, speech, and appearance, leading to profound functional impairments and psychological distress [4]. The treatment regimen for head and neck cancer often includes surgery, radiation therapy, chemotherapy, or a combination of these modalities, depending on the stage and location of the tumor. Treatment aims to control the disease and

*[1]Father Muller College of Physiotherapy, Mangalore, India. [2]Department of Medical Oncology, KS Hegde Medical Academy, NITTE (Deemed to be University), Mangalore, India. [3]Department of Radiation Oncology Father Muller Medical College, Mangalore, India. [4]THIM Internationale Hochschule für Physiotherapie, Landquart, Switzerland. [5]Nitte Institute of Physiotherapy, NITTE (Deemed to be University), Mangalore, India. [6]Biological, Physical and Exercise Sciences Department, Mount Vernon Nazarene University, Ohio, United States of America. [7]Department of Biochemistry, KS Hegde Medical Academy, NITTE (Deemed to be University), Mangalore, India. *For Correspondence: cheri8585@gmail.com*

prolong survival, but it is frequently accompanied by significant morbidity [5, 6].

Chemotherapy is a cornerstone in the treatment of head and neck cancer, particularly in advanced-stage disease where curative surgery may not be feasible. The primary role of chemotherapy is to shrink the tumor, control disease progression, and alleviate symptoms, either as a standalone treatment or in combination with radiation therapy (chemoradiotherapy). Chemotherapy is often used as part of concurrent chemoradiotherapy (CRT) to enhance the radiosensitivity of cancer cells, thereby improving the therapeutic effect of radiation [5, 7].

While chemoradiotherapy can be highly effective in managing head and neck cancer, its benefits come with a wide range of adverse effects [8]. Chemotherapeutic agents are non-specific, meaning they attack not only cancer cells but also healthy, rapidly dividing cells. This results in significant toxicity, leading to a host of side effects that severely impact the patient's physical and psychological well-being [8, 9].

The adverse effects of cancer treatment, particularly chemotherapy and radiotherapy, are numerous and can severely compromise a patient's overall health and quality of life [10]. Common side effects of chemotherapy include nausea, vomiting, fatigue, anemia, immunosuppression, and neuropathy. Radiation therapy can cause local toxicities such as skin burns, mucositis, dysphagia, and xerostomia (dry mouth), which are especially relevant in head and neck cancer patients [10-12]. The side effects of cancer treatment are not confined to immediate physical symptoms but also extend to critical physiological and psychological parameters such as decreased sleep quality, and overall quality of life [13].

Sarcopenia, or the loss of skeletal muscle mass and strength, is a significant complication in cancer patients, especially those undergoing chemotherapy and radiotherapy. In head and neck cancer patients, sarcopenia is exacerbated by treatment-related dysphagia and malnutrition, leading to rapid muscle depletion. This muscle loss is not only a marker of malnutrition but also an independent prognostic factor for poor outcomes, including decreased survival rates and a higher risk of treatment-related complications [14, 15].

Recent studies have reported that pretreatment sarcopenia is frequently prevalent in both HNC individuals [16-18]. Ameta-analysis reported that presence of pre-treatment sarcopenia has a significant negative impact on overall survival and relapse free survival in HNC compared with its absence [17]. In addition to this presence of pretreatment sarcopenia in HNC is considered to be a significant predictor of incomplete CRT or radiation breaks as they are more susceptible to chemo and radiation therapy induced toxicities than their non-sarcopenic counterparts [17-18]. Further clinically significant increase in the incidence of sarcopeniawas noted during the course of 7-week CRT program in Indian subjects [19]. Researches have reported that sarcopenia is a strong predictor of poor prognosis, poor disease specific survival rate contributing to worst survival outcomes in HNC patients receiving CRT [17-19]. Given the profound impact of treatment on sarcopenia, and overall quality of life, interventions aimed at mitigating these effects are crucial.

Exercise-based rehabilitation programs have emerged as promising strategies for improving outcomes in cancer patients [20]. A systematic review to evaluate the benefit of physical activity interventions on HNC patients, both during and following treatment, demonstrated an early evidence to support the benefits of physical activity in HNC [21]. Samuel et al in their study have observed that structured exercise based interventions have a positive effect functional capacity, and fatigue in HNC patients receiving CRT [22]. Progressive resistance training during CRT is proven to be feasible with favorable response to the training sessions [23, 24]. Structured exercise programs that incorporated combined training have been shown to improve muscle mass, strength, physical performance, and overall functional status in various groups of cancer patients. [25, 26] However, there is a dearth in the evidence regarding the effect of structured exercise programs consisting of combined aerobic and resistance training in head and neck cancer population.

The present randomized controlled trial (RCT) aimed at evaluating the effects of structured exercise-based rehabilitation on sarcopenia, and overall quality of life in head and neck cancer patients undergoing chemoradiotherapy.

Materials and Methods

Ethical Considerations

This study was a prospective, randomized controlled trial designed to assess the effects of structured exercise-based rehabilitation on sarcopenia, and quality of life in patients with HNC undergoing concurrent CRT. The study was conducted at Father Muller Medical College Hospital, involving patients who were diagnosed with locally advanced HNC (TNM stage III-IVb) and scheduled to receive CRT as part of their treatment protocol. The Father Muller Charitable Institutions Institutional Ethics Committee approved the study protocol, and the study adhered to the ethical standards outlined in the Declaration of Helsinki. All patients provided written informed consent after receiving a thorough explanation of the study's purpose, procedures, potential risks, and benefits. Participation was voluntary, and patients were allowed to withdraw at any time without consequences to their ongoing medical care.

Eligibility criteria

The inclusion criteria for this study was as following: adults aged 40-70 years, diagnosed with head and neck cancer (TNM stage III-IVb), patients receiving concurrent CRT, an Eastern Cooperative Oncology Group (ECOG) performance score of 0-2, indicating the patient was capable of performing self-care and participating in physical activity, and the ability to understand and provide informed consent. Exclusion criteria included a history of other cancers or previous HNC treatment, uncontrolled comorbid conditions (e.g., severe cardiac disease, uncontrolled diabetes, or severe chronic obstructive pulmonary disease), physical disabilities that precluded

participation in an exercise program, severe cognitive or psychiatric disorders, and any contraindication to participating in physical activity as determined by the treating physician.

Randomization

Computer generated random numbered table was used for sequencing Using block randomization, eligible patients were divided into two groups: Intervention and Control groups. The patients were divided into 5 blocks with 8 patients in each group. A sealed opaque envelope was used to conceal group information. This study followed the CONSORT guidelines [27].

Intervention

The intervention and control groups received exercise training according to their respective protocols. During the seven-week exercise training period in the hospital during chemoradiotherapy. The patients in both groups were closely watched for any complications on a daily basis.

Intervention Group

The intervention group received a combined aerobic and resistance exercise program during the course of chemo-radiotherapy for a period of seven weeks. The program was based on the exercise prescription recommended by American College of Sports Medicine (ACSM) guide lines [28], and protocol by Mustian et al. [29]. The exercises were performed at a frequency-5days/ week (except on the day of chemotherapy) and intensity of 3-5/10 RPE on modified Borg's scale for 15-20minutes. Aerobic exercise included brisk walking and resistance exercises included resistance band training for the major muscles of upper limb and lower limb done in two sets (1 set = 8 to 15 repetitions) The exercises consisted of biceps curl, triceps extension, overhead shoulder flexion, hip flexion, quadriceps (knee extension), and hip abduction.

Control Group

The control group was recommended to walk, 3 times10-mins during the day for 5 days a week which is 150mins/ week as recommended by National Comprehensive Cancer Network (NCCN) guidelines [30]. It was chosen as a low-intensity intervention aimed at maintaining basic physical activity levels during treatment. To make sure it stayed within the guidelines, the intensity of these sessions was tracked and kept between 3 and 5 on the modified Borg's scale. They were urged to continue being as active as they could.

Outcome measures

Outcome measure were evaluated on day before starting CRT and at 7 weeks after the end CRT. Upon enrolment, baseline data were collected from all patients, including demographic details, clinical history, and baseline functional status. The primary outcomes measured were sarcopenia, and quality of life.

Sarcopenia was assessed using three parameters: skeletal muscle mass, muscle strength, and physical performance. Skeletal muscle mass was measured using a Bioelectrical Impedance Analyzer (BIA) and the muscle strength was evaluated using a JAMAR hand dynamometer to measure handgrip strength. Physical performance was assessed using the Time-Up-and-Go test (TUG). Additionally, the six-minute walk distance (6MWD) test was used as a measure of overall functional capacity.

Quality of life was evaluated using the Functional Assessment of Cancer Therapy-Head & Neck (FACT-H&N) questionnaire, a validated instrument that measures physical, social, emotional, and functional well-being specifically in patients with head and neck cancer.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 26.0). Continuous variables, such as skeletal muscle mass, muscle strength, physical performance, and quality of life scores, were summarized as mean and standard deviation (SD). Categorical variables were expressed as percentages. The Wilcoxon signed-rank test was used to assess within-group differences and the Mann-Whitney U test was used for between-group comparisons. Effect sizes (ES) were calculated to determine the magnitude of differences observed between the two groups. Intention to treat analysis was used to address the dropouts. A p-value of <0.05 was considered statistically significant. Additionally, exploratory subgroup analyses were conducted to evaluate whether the intervention effects varied by age, gender, baseline fitness levels, and cancer stage.

Results

The results of this randomized controlled trial provide valuable insights into the effects of structured exercise-based rehabilitation on sarcopenia, and overall quality of life among head and neck cancer patients undergoing chemo-radiotherapy. A total of 80 head and neck cancer patients undergoing chemo-radiotherapy participated in the study, with 40 individuals assigned to Control Group (walking-based exercise) and 40 to Intervention Group (combined aerobic and resistance training). The demographic analysis revealed that the two groups were at baseline. The characteristics of the study population are represented in Table 1 and 2.

The study revealed significant differences in outcomes related to sarcopenia, quality of life, and functional capacity between the two groups and are shown in Table 3.

Table 1. Characteristics of the Study Population

		Control Group	Intervention Group	p value
Age in Years (Mean±SD)		54.59±11.10	54.26±10.43	0.899
Gender Frequency (%)	Female	7 (17.5)	11 (27.5)	0.43
	Male	33 (82.5)	29 (72.5)	

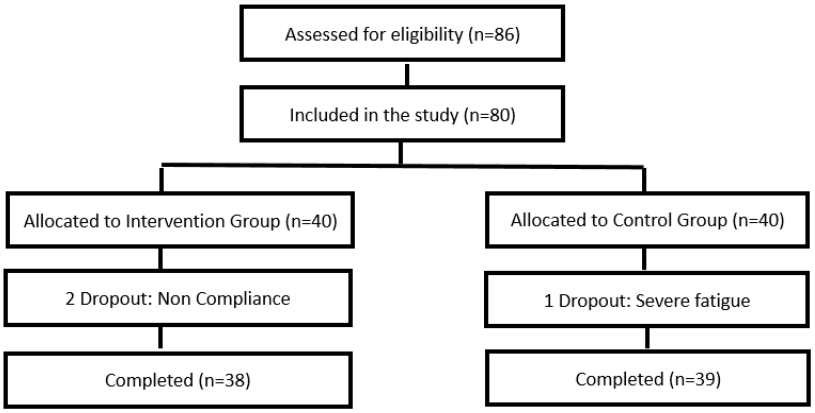

Figure 1. CONSORT Flow Diagram

Table 2 Distribution of Cancer Types Among Study Participants

	Control Group	Intervention Group	Total
Ca Buccal Mucosa	11	6	17
Ca Base of Tongue	3	2	5
Ca Circoid	1	2	3
Ca Floor of Mouth	1	4	5
Ca Glottis	1	1	2
Ca hard palate	0	2	2
Ca Larynx	2	4	6
Ca Maxilla	2	3	5
Metastasis of Unknown Origin of Neck	0	1	1
Ca Nasopharynx	1	1	2
Ca Oropharynx	1	3	4
Ca Parotid	2	0	2
Ca RMT	3	0	3
Ca Alveolus	1	0	1
Ca Supraglottis	1	2	3
Ca Tongue	10	8	18
Ca Tonsil	0	1	1

The progression of sarcopenia, as measured by skeletal muscle mass and handgrip strength, indicated a notable divergence between the groups. Intervention Group showed a smaller decrease in total skeletal muscle mass compared to Control Group, with Intervention Group's total skeletal muscle mass decreasing from 35 to 30 and Control Group's muscle mass decreasing from 40 to 21, both with significant p-values of <0.001. The effect size in Intervention Group (0.872) was larger, indicating that resistance training had a more positive impact on muscle retention compared to walking alone. Handgrip strength in both hands also demonstrated that Control Group experienced a more pronounced decline, particularly in the right hand, with a large effect size of 0.871, while Intervention Group showed a smaller, non-significant reduction in both hands.

Quality of life, assessed by the FACT-H&N questionnaire, showed significant improvement in Control Group from 66 to 61 ($p < 0.001$) with a large effect size of 0.724. In contrast, Intervention Group's quality of life saw a minor, non-significant change from 62 to 61. Despite Intervention Group's better physical outcomes, the impact on perceived quality of life was more evident in Control Group (Figure 1).

Functional capacity, measured by the Timed-Up-and-Go (TUG) test and the Six-Minute Walk Test (6MWT), demonstrated clear advantages for Intervention Group. Intervention Group showed significant improvements in both the TUG (from 7.45 to 6.50) and the 6MWT (from 420 to 480 meters), with large effect sizes of 0.773 and -0.838, respectively. In contrast, Control Group exhibited a decline in TUG performance, with times increasing from 7.60 to 13.00 seconds, and a moderate improvement in the 6MWT (from 370 to 420 meters). The overall results convey that resistance training significantly improved outcomes in Intervention Group compared to walking alone in Control Group. This suggests that although Control Group saw greater declines in physical parameters, participants may have experienced improvements in other areas, such as emotional or social well-being, potentially contributing to a better overall perception of quality of life.

Discussion

Head and neck cancers (HNC) are among the most challenging malignancies to treat due to their complex location, aggressive nature, and the profound impact they have on patients' quality of life. The management of HNC often involves multimodal treatments such as surgery, radiation therapy, and chemotherapy, all of which can lead to severe side effects that affect not only physical health but also functional abilities and psychological well-being thus affecting quality of life [31, 32].

Sarcopenia, and a decline in overall quality of life are well-documented adverse effects of cancer treatment, particularly in those receiving concurrent chemo-radiotherapy (CRT) [14]. Exercise-based interventions, particularly those incorporating resistance training, have been shown to mitigate some of these negative effects by

Table 3. Comparison of FACT-H&N, Hand Grip Strength, Total Skeletal Muscle, and BMI Pre- and Post-Intervention

		PRE CRT	POST CRT	WSRT	ES
Sarcopenia	Intervention Group	1	3	<0.001	-0.83
	Control Group	1	4	<0.001	0.871
	p	0.012	<0.001		
	Effect Size	-0.301	-0.827		
Hand Grip Right	Intervention Group	29 (4.448)	28 (2.965)	0.269	
	Control Group	28 (2.965)	20 (1.483)	<0.001	0.871
	p	0.637	<0.001		
	Effect Size	0.066	0.85		
Hand Grip Left	Intervention Group	28	26	0.108	
	Control Group	30	20	<0.001	0.871
	p	0.526	<0.001		
	Effect Size	0.089	0.864		
Total Skeletal Muscle	Intervention Group	35 (10.230)	30 (10.378)	<0.001	0.872
	Control Group	40 (7.413)	21 (4.893)	<0.001	0.871
	p	0.515	<0.001		
	Effect Size	-0.092	0.766		
Body Mass Index (BMI)	Intervention Group	23 (2.076)	20 (2.965)	<0.001	0.858
	Control Group	24 (1.483)	20 (1.927)	<0.001	0.871
	p	0.168	0.239		
	Effect Size	-0.194	-0.165		
Functional Assessment of Cancer Therapy – Head & Neck (FACT-H&N)	Intervention Group	62 (8.896)	61 (10.030)	0.163	
	Control Group	66 (8.896)	61 (11.501)	<0.001	0.724
	p	0.11	0.644	.	
	Effect Size	-0.224	0.065		
Timed Up and Go (TUG) (sec)	Intervention Group	7.45 (1.400)	6.50 (1.039)	<0.001	0.773
	Control Group	7.60 (1.334)	13.00 (1.779)	<0.001	-0.871
	p	0.757	<0.001		
	Effect Size	-0.044	-0.99		
6 Minute Walk Test (6MWT) (m)	Intervention Group	420 (74.130)	480.00 (88.956)	<0.001	-0.838
	Control Group	370.00 (44.478)	420.00 (70.423)	<0.001	-0.79
	p	0.031	0.006		
	Effect Size	0.302	0.385		

improving muscle mass, strength, and physical function, as well as enhancing overall well-being [33, 34].

The present randomized controlled trial was designed to evaluate the effect of structured exercise-based rehabilitation on sarcopenia, functional capacity and quality of life in HNC patients undergoing CRT, comparing a walking-only program with a combined aerobic and resistance training program. In this study, the results highlighted a clear distinction between the two groups in terms of muscle preservation. Intervention Group, which engaged in a combined aerobic and resistance training regimen, exhibited a significantly smaller decrease in skeletal muscle mass compared to Control Group, which participated in walking-based exercise only.

Handgrip strength, another key indicator of sarcopenia, further demonstrated the benefits of resistance training. Control Group experienced a substantial decline in both right and left-hand grip strength, indicating a marked reduction in muscle strength. In contrast, Intervention Group showed only a minor, non-significant reduction in grip strength, particularly in the right hand. These findings align with existing literature that emphasizes the role of resistance training in countering muscle atrophy and preserving muscle function in cancer patients [35].

Sarcopenia was lesser in the aerobic and resistance training group when compared to the control. The difference in effect sizes between the two groups highlights the favourable impact of resistance training on muscle mass and strength. In Samuel et al.'s study [35], although sarcopenia was not directly measured, the exercise group showed improvements in muscle mass preservation, inferred through enhanced functional capacity over 11 weeks. This aligns with the current study's findings, indicating that structured exercise can mitigate sarcopenia in HNC patients undergoing CRT, with more intensive programs delivering better outcomes. Similarly, Avancini et al.'s systematic review [36] found that combined aerobic and resistance training resulted

in improvements in skeletal muscle mass and strength, suggesting that multimodal exercise programs are more effective in combating sarcopenia compared to resistance training alone, corroborating the benefits of combining both exercise types as seen in the present study.

In contrast, Pérez et al.'s meta-analysis [37] reported mixed results regarding muscle strength, with progressive resistance training (RET) yielding more consistent improvements in lower limb strength than in upper limb strength, highlighting a smaller overall effect of RET. This aligns with our findings, where lower-body exercises showed more prominent improvements. While Satish et al.'s study [38] did not assess sarcopenia directly, their focus on functional capacity and grip strength revealed moderate improvements in muscle maintenance with multimodal exercise, reinforcing the current study's conclusions on the importance of resistance training for muscle preservation.

Resistance training directly stimulates muscle hypertrophy by inducing mechanical and metabolic stress, which activates anabolic pathways and promotes muscle protein synthesis, thereby mitigating the effects of sarcopenia. This is critical for cancer patients, as muscle mass and strength are strong predictors of overall survival and treatment tolerance.

In present study, Quality of life, as measured by the FACT-H&N questionnaire, yielded somewhat surprising results. It was Control Group that demonstrated significant improvements in quality of life as compared to Intervention Group. This divergence suggests that quality of life is a multifaceted construct that may not be directly correlated with physical improvements alone.

In a review by Pérez IMM et al. [37], several studies highlighted improvements in quality of life among HNC survivors undergoing CRT through multimodal exercise interventions, combining aerobic, resistance, and flexibility exercises. However, the meta-analysis presented a weak recommendation for exercise in improving quality of life due to the heterogeneity across studies. This contrasts with our study, where walking alone significantly enhanced quality of life, suggesting that even low-intensity exercise may be effective in improving overall well-being in HNC patients. Similarly, Avancini A et al.'s review [36] noted improvements in quality of life through combined aerobic and resistance training, though not all trials observed significant changes. Our findings support the idea that even low-to-moderate intensity exercises, like walking, can sufficiently boost psychological components of quality of life without drastically affecting physical fitness.

Satish et al. [38] further corroborated this, showing that structured exercise programs led to significant improvements in global health status, physical functioning, and cognitive functioning, with moderate effect sizes, while the control group saw a decline in these areas. This resonates with the present study, where structured exercise produced better outcomes in both mental and physical Quality of life components. Similarly, Samuel et al.'s study [35], which used the SF-36 questionnaire, found significant increases in both Physical and Mental Component Scores after 11 weeks of combined aerobic and resistance training, suggesting that more comprehensive and prolonged exercise interventions can yield substantial improvements in quality of life across both physical and mental domains in HNC patients.

Lastly in present study functional capacity, assessed through the Timed-Up-and-Go (TUG) test and the Six-Minute Walk Test (6MWT), demonstrated clear advantages for Control Group, reflecting the efficacy of combined aerobic and resistance training in improving mobility and endurance. These improvements suggest that resistance training, in combination with aerobic exercise, enhances both mobility and cardiovascular endurance, which are critical components of functional capacity in cancer patients.

On the contrary, the decline in TUG performance in Intervention Group suggests that walking alone may be insufficient to counteract the negative effects of CRT on mobility and balance. The TUG test is a measure of dynamic balance and lower-body strength, both of which are heavily impacted by muscle loss and fatigue. Without the inclusion of resistance training, Intervention Group participants likely experienced greater muscle loss, leading to a decline in functional mobility. Samuel SR et al. [35] found that after an 11-week exercise program, participants in the exercise group improved their 6MWT distance by 37 meters, while the control group experienced a significant decline of 73 meters. This highlights the impact of exercise in preserving and enhancing functional capacity during and after CRT, aligning with the present study's findings These results emphasize the role of structured exercise in maintaining mobility and endurance in cancer patients undergoing intensive treatments like CRT. Satish et al. [38] similarly demonstrated that their experimental group achieved better 6MWT results post-treatment, corroborating the moderate effect size for functional improvements seen in structured exercise programs across studies.

The findings of this study have important implications for the design of rehabilitation programs for HNC patients undergoing CRT. The superior performance of the combined aerobic and resistance training regimen in preserving muscle mass, improving functional capacity, and reducing sarcopenia underscores the importance of including resistance training in cancer rehabilitation programs.

This study has several strengths, including its randomized controlled design, the use of objective measures for sarcopenia and its focus on a vulnerable population with significant treatment-related side effects. However, there are also limitations to consider. The study's relatively short duration may have limited the ability to fully capture long-term benefits or potential delayed effects of the interventions on quality of life.

In conclusion, sarcopenia was lesser in the Intervention Group compared to the Control Group. However, Control Group that demonstrated significant improvements in quality of life as compared to Intervention Group. Therefore thos is study demonstrates that structured exercise-based rehabilitation, particularly incorporating resistance training, can play a crucial role in mitigating the adverse effects of CRT in head and neck cancer

patients. These findings highlight the importance of integrating exercise into routine cancer care to improve patient outcomes and suggest that more intensive exercise regimens may offer greater benefits in terms of physical performance, and muscle preservation. Further research is needed to explore the optimal balance between exercise intensity and quality of life and to investigate the long-term effects of exercise interventions in this population.

Author Contribution Statement

All authors contributed to the by contributing to the Protocol writing, Data Collection and Interpretation, Writing and approving the manuscript

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Ethical Approval

This study was approved by Father Muller Institutional Ethics Committee

Availability of Data

Data will be available at request with the corresponding author

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