FULL STUDY PROTOCOL, STATISTICAL ANALYSIS PLAN (SAP) & INFORMED CONSENT FORMS (ICF)

Impact of Verbal Cueing in Multimodal Exercise Rehabilitation: A Retrospective Study in Breast Cancer Survivors Undergoing Radiation Therapy

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1. Personnel

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2. Introduction

2.1 Background & Aims

Breast cancer is one of the most prevalent malignancies affecting women worldwide, and advances in treatment modalities such as surgery, chemotherapy, and radiation therapy have substantially improved survival rates. However, despite improved prognosis, many survivors experience persistent long-term physical and psychological complications following treatment. Reduced shoulder range of motion (ROM), cancer-related fatigue (CRF), and heightened stress levels are among the most commonly reported adverse outcomes. These complications are often the result of radiation-induced fibrosis, post-surgical scarring, muscular tightness, and systemic fatigue, with elevated cortisol levels serving as a physiological indicator of chronic stress. Collectively, these impairments negatively affect functional independence, limit participation in daily activities, and reduce overall quality of life among breast cancer survivors.

Exercise has emerged as a safe, effective, and non-pharmacological strategy to address many of these treatment-related sequelae. Multimodal exercise programs incorporating aerobic training, resistance exercises, flexibility training, and mind–body components have demonstrated beneficial effects on physical function, fatigue reduction, and stress modulation in cancer populations. Nevertheless, the effectiveness of these programs may vary depending on factors such as program delivery, patient engagement, and the quality of instruction provided during exercise sessions. Verbal cueing defined as structured linguistic instructions, motivational prompts, and corrective feedback delivered during exercise—has been shown in sports science and rehabilitation literature to enhance motor learning, improve biomechanical performance, increase adherence, and optimize exercise outcomes. By directing attention, reinforcing correct movement patterns, and promoting motivation, verbal cues may play a critical role in maximizing the therapeutic benefits of exercise interventions.

Despite the growing evidence supporting exercise-based rehabilitation, limited research has specifically examined the added value of verbal cueing in exercise programs for breast cancer survivors, particularly those undergoing radiation therapy. This period is often associated with heightened fatigue, increased stress, and progressive musculoskeletal impairments, including shoulder stiffness and reduced ROM. Radiation therapy, while essential for cancer control, can exacerbate joint pain, muscle tightness, and systemic exhaustion, thereby contributing to elevated cortisol levels that may further impair recovery and overall health. Although multimodal exercise interventions have shown promise in improving functional outcomes and regulating stress biomarkers in various clinical populations, their specific effects particularly when delivered with structured verbal cues remain insufficiently explored in radiation-treated breast cancer survivors.

The need for targeted and comprehensive rehabilitation strategies in this population is increasingly evident due to the rising global incidence of breast cancer and the growing number of long-term survivors. A high prevalence of shoulder dysfunction, upper limb impairment, postural abnormalities, pain, lymphedema, and reduced quality of life has been documented following multimodal cancer treatments. Moreover, there is limited emphasis on structured physiotherapy programs that simultaneously address shoulder function, cancer-related fatigue, and psychological stress, as well as a lack of evidence examining the combined effects of such interventions on functional, subjective, and physiological outcomes. Exercise-based rehabilitation and targeted physiotherapy represent cost-effective and accessible approaches to restoring shoulder mobility, reducing fatigue, and improving quality of life. The use of validated and objective outcome measures, such as active shoulder ROM and salivary cortisol levels, further strengthens the clinical relevance and translational significance of such interventions.

Accordingly, the aim of the present study is to evaluate the effectiveness of a multimodal exercise program delivered with and without verbal cues on shoulder range of motion, cancer-related fatigue, and cortisol levels in breast cancer survivors undergoing radiation therapy.

2.2 Background Literature Review

Rao et al. (2025) described the anatomy and physiology of the human breast, explaining its complex structure and the changes it undergoes throughout life, from development in the womb to puberty, pregnancy, lactation, and menopause. The authors highlighted the importance of understanding breast components such as lobules, ducts, connective tissue, lymphatic drainage, and blood supply, as this knowledge is essential for accurate diagnosis, treatment planning, and effective management of breast diseases[(1)].

Xiong et al. (2025) discussed the diverse and heterogeneous nature of breast cancer, focusing on the role of genetic changes, molecular subtypes, and biological mechanisms in disease progression. Their review emphasized recent advances in precision medicine, including targeted therapies and AI-assisted diagnostic tools, which support personalized treatment approaches and improve long-term survivorship outcome [(2)].

Zhang et al. (2025) examined global breast cancer trends using GLOBOCAN 2022 data and reported that breast cancer is the most common cancer among women worldwide. The study highlighted major regional differences, with higher incidence rates in developed countries and higher mortality in developing regions, particularly South-Central Asia and India. These findings stress the need for better early detection, access to care, and comprehensive treatment strategies[(3)].

Gupta et al. (2025) showed that structured exercise programs significantly improve the quality of life of breast cancer patients and survivors. Their analysis demonstrated improvements in physical, emotional,

and functional well-being, emphasizing the importance of including exercise-based rehabilitation as part of routine survivorship care[4].

Murena et al. (2025) conducted a retrospective analysis of 67 breast cancer patients who underwent mastectomy followed by reconstruction and adjuvant therapy to examine scapular dyskinesis. A high prevalence was reported, with static dyskinesis in 64.2% and dynamic dyskinesis in 73.1% of patients, including notable bilateral involvement. The study found that surgical technique and rehabilitation exposure significantly influenced shoulder outcomes, with longer physiotherapy duration reducing the risk of dynamic dyskinesis and prepectoral reconstruction showing better scapular mechanics. These findings underscore the importance of early and sustained physiotherapy to prevent long-term shoulder dysfunction in breast cancer survivors[5].

3. Study Protocol

3.1 Research Design Outline

The study was conducted as a completed clinical trial among breast cancer survivors undergoing radiation therapy at Saveetha Medical College and Hospital.

Initially titled “Impact of Verbal Cueing in Multimodal Exercise Rehabilitation: A Retrospective Study in Breast Cancer Survivors Undergoing Radiation Therapy,” the trial successfully evaluated the effectiveness of a multimodal exercise rehabilitation program delivered with verbal cueing compared to the same program delivered without verbal cueing.

Participants who were undergoing radiation therapy were allocated into two groups: one group received the multimodal exercise program accompanied by structured verbal cues, while the comparison group performed the same exercise program without verbal guidance. Upon completion of the intervention period, outcomes were assessed to determine the impact of verbal cueing on physical and physiological parameters.

The outcome measures included shoulder range of motion, cancer-related fatigue, and

physiological stress levels. Shoulder range of motion was measured using a universal goniometer for shoulder flexion, abduction, and external rotation. Cancer-related fatigue was evaluated using the FACIT–Fatigue scale, and physiological stress was assessed through salivary cortisol analysis.

Participants

Breast cancer survivors undergoing radiation therapy from Saveetha medical college and hospital attended the study setting will be eligible to participate in this study.

3.3 Recruitment

All breast cancer survivors undergoing radiation therapy and attending the study setting were enrolled in the clinical trial after meeting the eligibility criteria. Participant information sheets and informed consent forms were provided to all eligible individuals, detailing the purpose of the study, intervention procedures, and inclusion and exclusion criteria. Participants who consented to participate were enrolled in the trial and underwent baseline assessments prior to the initiation of the intervention.

Baseline evaluations included assessment of shoulder range of motion using a universal goniometer, cancer-related fatigue assessment using the FACIT–Fatigue scale, and evaluation of physiological stress through salivary cortisol analysis. Written informed consent was obtained from all participants, and signed consent forms were collected and retained by the site principal investigator before the commencement of any study-related procedures.

3.3Administration

TABLE- 1(MMV protocol)

Phase	**Activities**
1. Warm-Up	- Marching in place

(5 – 10 minutes)	- Arm swings and ankle pumps - Neck and shoulder rolls
2. Aerobic exercise (15 – 20 minutes)	-Walking depending on progress and tolerance or -Cycling
3. Resistance Training (15 – 20 minutes)	- Bodyweight (push-ups, squats, lunges) - Resistance bands/light weights (bicep curls, shoulder press, leg extensions). - Progression: Gradually increase reps, sets, or intensity as tolerated.
4. Flexibility and Stretching (5 to 10 minutes)	Static stretching: Shoulders, elbows, wrists, quadriceps, hamstrings, and calves. Hold each stretch for 15-30 seconds.
5.Relaxation and Cool down (5 – 10 minutes)	- Deep breathing, - Ankle pumps and - Neck/ Shoulder rolls

Assessment & Outcomes Measures

3.1.1 Primary outcomes

Shoulder Range of Motion (ROM)

Shoulder range of motion was evaluated as a primary functional outcome measure, with particular emphasis on shoulder flexion, abduction, and external (lateral) rotation of the affected upper limb. These movements are critical for performing overhead activities, self-care tasks, and functional reaching, and are commonly restricted in breast cancer survivors due to radiation-induced fibrosis, post-surgical scarring, pain, and muscle tightness.

Active ROM was measured using a standard universal goniometer, following established anatomical landmarks and standardized testing positions to ensure accuracy and reproducibility. Assessments were conducted at baseline prior to the initiation of the exercise intervention and repeated at the end of the intervention period.

Improvements in shoulder flexion, abduction, and external rotation following the intervention indicate enhanced joint mobility, improved soft-tissue extensibility, and better functional use of the upper limb. Goniometric assessment of shoulder ROM is widely accepted in clinical and research settings and has demonstrated high intrarater and interrater reliability, making it a valid and responsive tool for evaluating changes in shoulder function in oncological rehabilitation populations.

3.1.2 Secondary outcomes

Cancer-related fatigue was assessed using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–F) Scale, a validated, self-administered questionnaire specifically developed to evaluate fatigue

and its impact on daily functioning in individuals with chronic illnesses, including cancer. The FACIT–F consists of 13 items rated on a 5-point Likert scale ranging from 0 (“not at all”) to 4 (“very much”), with total scores ranging from 0 to 52.

o Higher FACIT–F scores indicate lower levels of fatigue and better functional well-being. Participants completed the questionnaire at baseline and after completion of the intervention period.

o Cancer-related fatigue is one of the most common and persistent symptoms experienced by breast cancer survivors undergoing radiation therapy and can markedly affect physical performance, emotional health, and overall quality of life. The FACIT–Fatigue Scale has demonstrated excellent reliability, validity, and sensitivity to change in oncology populations, making it an appropriate and responsive outcome measure for evaluating the effectiveness of exercise-based rehabilitation interventions.

Salivary Cortisol Level

Physiological stress response was evaluated through the measurement of salivary cortisol levels, a non-invasive biomarker that reflects hypothalamic–pituitary–adrenal (HPA) axis activity. Saliva samples were collected under standardized conditions to minimize the effects of diurnal variation in cortisol secretion.

Samples were obtained at consistent times of the day at baseline and after completion of the intervention period to ensure comparability of results.

Elevated salivary cortisol levels are commonly associated with chronic stress, fatigue, and altered neuroendocrine regulation in breast cancer survivors undergoing radiation therapy. A reduction or normalization of cortisol levels following the intervention indicates improved stress regulation, enhanced autonomic balance, and better physiological adaptation to treatment-related stress.

[Time Frame: Baseline and post-intervention]

4. Statistical Analysis Plan (SAP)

The statistical analysis will be performed using IBM SPSS Statistics version 27. The study was conducted on breast cancer survivors aged 35 - 45 years undergoing or recently completing radiation therapy. The primary objective of the study was to compare the effects of two intervention protocols between Group A (MMV – Multimodal Exercise with Verbal Cues) and Group B (MMWV – Multimodal Exercise without Verbal Cues) on shoulder joint range of motion, fatigue, and salivary cortisol levels.

4.1 Primary Outcome

The primary outcome measures included shoulder range of motion, specifically shoulder flexion, shoulder abduction, and external rotation, measured using a goniometer.

4.2 Secondary outcome

The secondary outcome measures were fatigue, assessed using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACT-F) scale, and salivary cortisol levels, measured in ng/mL.

A total of 36 participants were included in the study and were equally allocated into two groups, with 18 participants in Group A and 18 participants in Group B. Descriptive statistics were expressed as mean ± standard deviation (SD). Inferential statistical analysis will include tests of normality, homogeneity of variance, paired sample t-tests for within-group comparisons, and independent sample t-tests for between-group comparisons. The level of statistical significance was set at $p < 0.05$.

4.3 Missing Data

For breast cancer survivors who did not attend the scheduled assessment sessions, mean imputation of the corresponding outcome scores from their respective intervention group was applied to

manage missing data.

Informed Consent Forms (ICF)

Written informed consent was obtained directly from all breast cancer survivors participating in the study using the approved consent forms provided with the study protocol.

4.4 Rights and Risks to participants

Rights

Participants had the right to withdraw from the study at any time without providing any explanation. They were free to decline or refrain from answering any questions related to the study procedures. Participants also had the right to seek clarification and ask questions regarding the assessments or intervention procedures at any stage of the study, either before commencement or during the course of assessments and interventions. Participation in the study was entirely voluntary and did not involve any remuneration or reimbursement.

Risks

Researcher does not anticipate any risk from this research study.

4.5 Privacy and Confidentiality

All breast cancer survivors enrolled in the study were de-identified and assigned a unique identification (ID) number at the time of enrollment, which was recorded by the study administration personnel at the study site. All personal and clinical data were handled confidentially and used solely for research purposes. Any assessment records and biological samples collected for analysis were securely stored and were not shared outside the research team, in accordance with the ethical guidelines and policies of the study institution.

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