Study Protocol and Statistical Analysis Plan

Official Title: Integrating Clinical Psychology Into the Care of Patients With Head and Neck Cancer: A Pilot Randomized Controlled Trial

Brief Title:
Clinical Psychology and Biofeedback in Patients With Head and Neck Cancer

ClinicalTrials.gov Identifier:
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Background

Head and neck cancer encompasses oncological conditions that can develop in several anatomical sites, including the oral cavity, pharynx, larynx, nasal cavity, and salivary glands (Luckett et al., 2011). In particular, oral cavity cancer, including cancers of the lips, tongue, floor of the mouth, cheeks, gums, and palate, is a major cause of cancer-related mortality worldwide and is characterized by facial disfigurement and functional impairment, with a five-year survival rate of approximately 50% (Cancer Statistics Center - American Cancer Society, 2024; Tranby et al., 2022). Approximately 35,310 new cases of oral cavity cancer are diagnosed annually in the United States, and approximately 67,000 new cases occur in the European Union (Cancer Statistics Center - American Cancer Society, 2024; Graillon et al., 2022).

Treatment for head and neck cancer may include demolitive and/or reconstructive surgery, radiotherapy, chemotherapy, and immunotherapy. These treatments may result in difficulties with eating, swallowing, and speaking, as well as alterations in body image, with significant consequences for patients' psychological well-being and quality of life (Tang et al., 2023; Mascarella et al., 2022; Kangas et al., 2013). The literature highlights the presence of anxiety, post-traumatic stress symptoms, and depressive symptoms among patients with head and neck cancer (Tang et al., 2023; Kassir et al., 2021).

Within an integrated care perspective, it is essential to consider how both the oncological disease and its treatments may affect patients' somatopsychic balance and their ability to perceive, communicate, work, and maintain meaningful relationships (Franzoi et al., 2023; Scherl et al., 2020; Granieri et al., 2018). In particular, integrating clinical psychological interventions that focus on the somatic and psychological aspects of illness experience and psychophysiological processes may represent a valuable approach (Burch et al., 2020; Ehrenreich & Rolnick, 2019; Schore, 2022).

However, the literature shows a lack of empirically validated psychological interventions specifically targeting patients with head and neck cancer (Kangas et al., 2013).

Planned Study

This study is a pilot randomized controlled clinical trial evaluating the efficacy and feasibility of a brief clinical psychological intervention including biofeedback techniques to reduce post-traumatic stress symptoms and somatopsychic distress in patients undergoing demolitive surgery of the oral cavity or oropharynx, with or without simultaneous flap reconstruction.

Objectives of the Study

The primary objective of this study is to evaluate the short-term efficacy of a brief clinical psychological intervention, including biofeedback techniques, in reducing post-traumatic stress symptoms in patients undergoing demolitive surgery of the oral cavity or oropharynx, with or without simultaneous flap reconstruction.

Secondary objectives are:

To compare the effects of the psychological intervention on somatopsychic distress and quality of life in patients undergoing oral cavity or oropharyngeal surgery, with or without simultaneous flap reconstruction.
To evaluate the persistence over time of the effects of the psychological intervention in patients with and without simultaneous flap reconstruction.
To examine the impact of flap reconstruction on quality of life and somatopsychic distress after surgery, regardless of assignment to the psychological intervention.

Endpoints
Primary Endpoint

- Mean total score on the Impact of Event Scale-Revised (IES-R) after surgery.
- Secondary Endpoints
- Mean total score on the Hyperarousal subscale of the IES-R.
- Mean total score on the Body Image Scale (BIS).
- Mean score on the Global Health Status scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).
- Mean scores on the Social Eating, Social Contact, and Less Sexuality scales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Head and Neck (EORTC QLQ-H&N35).
- Mean total score on the Clinical Outcomes in Routine Evaluation – Outcome Measure (CORE-OM).
- Proportion of participants completing the intervention.
- Proportion of participants completing all assessments.

Design

This is a randomized, controlled, non-pharmacological pilot study involving adult patients with head and neck cancer scheduled to undergo demolitive surgery of the oral cavity or oropharynx, with or without simultaneous flap reconstruction.

Participants will be randomly assigned to either the experimental group or the control group. Each participant will receive a unique identification number at the time of randomization.

After eligibility confirmation and written informed consent, participants will be stratified according to predefined criteria before randomization. Allocation will be performed using variable block randomization.

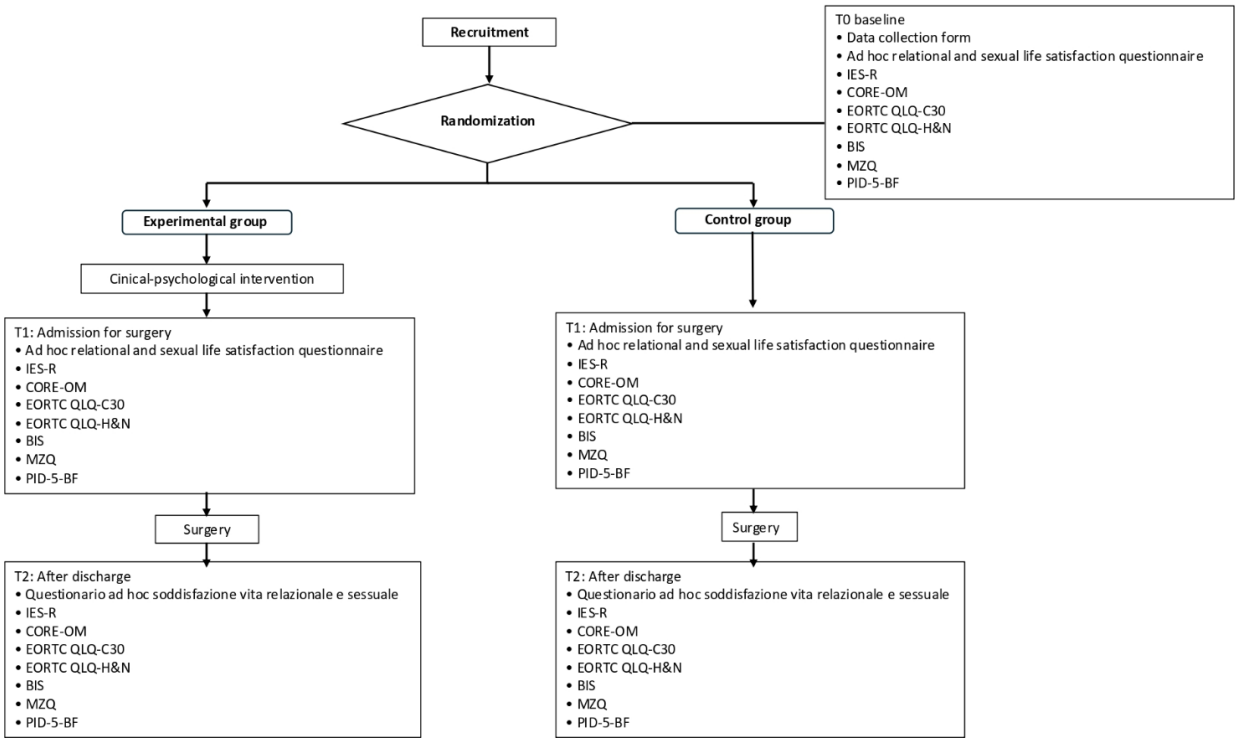
Stratification criteria will include:

Sex: male vs female.
Type of surgery: with vs without simultaneous flap reconstruction.

This approach aims to ensure balance between groups and reduce potential bias.

Research staff involved in randomization and delivery of the psychological intervention will be aware of treatment allocation. Outcome assessors and other study personnel will remain blinded to group allocation. Participants will be instructed not to disclose their study group assignment to other patients.

Survey scheme



Participants

The study will recruit adult patients with head and neck cancer scheduled to undergo demolitive surgery of the oral cavity or oropharynx, with or without simultaneous flap reconstruction, at the Head and Neck Cancer Unit of ASL Città di Torino, Italy.

Each participant will receive the study information sheet and provide written informed consent before enrolment.

The study does not modify the medical and surgical treatment planned according to standard clinical practice.

Eligibility Criteria:

Inclusion Criteria

Participants must meet all of the following criteria:

Diagnosis of head and neck cancer and scheduled to undergo:

- demolitive surgery of the oral cavity or oropharynx without simultaneous flap reconstruction;

- demolitive surgery of the oral cavity or oropharynx with simultaneous flap reconstruction.
- Age ≥18 years at the time of informed consent.
- Italian language proficiency.

Exclusion Criteria
Participants will be excluded if they:
- Are unable to provide written informed consent.
- Have a diagnosed psychiatric disorder.
- Have a diagnosed neurocognitive disorder.
- Are currently undergoing psychological or psychotherapeutic treatment.

Interventions Groups

All eligible participants who agree to participate will complete baseline assessment (T0).
After T0 assessment, participants will be randomized into two groups:
- Experimental group: receives a brief clinical psychological intervention including biofeedback techniques.
- Control group: receives standard care without the study psychological intervention.
Participation in the study is not compatible with initiation of psychological or psychotherapeutic treatment during the study period. If a need for psychological or psychotherapeutic care emerges during the study, the participant will discontinue participation.

Sample Size Calculation

In 2023, approximately 50 patients underwent demolitive surgery of the oral cavity or oropharynx at the Head and Neck Cancer Unit of ASL Città di Torino, including 30 patients without and 20 patients with simultaneous flap reconstruction.
Assuming a 15% annual increase in the number of surgical procedures and a clinically relevant difference corresponding to an effect size of 0.5 standard deviations between groups, the estimated sample size is 29 participants per group. With a one-tailed significance level of $\alpha=0.15$, the study is expected to have 80% statistical power.
Description of the Brief Clinical Psychological Intervention Including Biofeedback Techniques

The intervention consists of two clinical psychological sessions based on a psychoanalytic framework, each lasting approximately 60 minutes, integrating biofeedback techniques. Sessions will be audio-recorded and transcribed verbatim.

First Session

During the first session, the clinician explores the participant's illness history, focusing on the impact of disease-related changes on emotions, thoughts, and interpersonal relationships. Participants are invited to share relevant aspects of their personal history in relation to the experience of illness and treatment.
The clinician explores the participant's awareness of the diagnosis, planned surgery, and expected postoperative course, while identifying psychosocial vulnerabilities and resources. Particular attention is given to aspects of body image, identity, and areas of personal investment that may be affected by surgery, as well as preserved resources that may support adaptation.
The clinician provides psychoeducation on the relationship between emotional states and bodily responses, explaining how changes in psychophysiological activation may contribute to emotional regulation.
A three-minute baseline biofeedback recording is then performed to assess psychophysiological parameters, including respiratory rate, heart rate, heart rate variability, surface electromyography, peripheral temperature, and skin conductance. After psychoeducation on diaphragmatic breathing, the clinician guides the participant in practicing slow and deep breathing with the support of biofeedback monitoring, with the aim of promoting bottom-up self-regulation strategies. At the end of the session, an additional three-minute biofeedback recording is performed. Participants are informed about the usefulness of home practice and are encouraged to perform daily diaphragmatic breathing exercises lasting approximately 10–20 minutes. When possible, participants are encouraged to use the free "Paced Breathing" application to support breathing training with a target of approximately six breathing cycles per minute. Informative material on diaphragmatic breathing is also provided.

Second Session

The second session includes an exploration of thoughts, emotions, and bodily sensations that may have emerged following the first session and home practice. Participants undergo a three-minute recording of psychophysiological parameters, followed by a biofeedback session focused on diaphragmatic breathing. The clinician explores any changes in participants' expectations, emotions, and perceptions regarding surgery and postoperative recovery since the first session. At the end of the session, a further three-minute baseline biofeedback recording is performed.

Administration Timing

Assessments will be performed at the following time points:

- T0 (Baseline): when the participant is placed on the waiting list for demolitive surgery of the oral cavity or oropharynx, with or without simultaneous flap reconstruction.
- T1: at hospital admission for surgery.
- T2: at the post-discharge follow-up visit after surgery.

Clinical and Psychological Assessments

At each assessment time point, the following measures will be collected:

- Socio-demographic and clinical data.
- Ad hoc questionnaire assessing satisfaction with relational and sexual life.
- Impact of Event Scale-Revised (IES-R): self-report measure assessing post-traumatic stress symptoms.
- Body Image Scale (BIS): self-report measure assessing body image concerns.
- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30): measure of health-related quality of life in cancer patients.
- EORTC Quality of Life Questionnaire-Head and Neck (EORTC QLQ-H&N35): measure of quality of life specific to head and neck cancer patients.
- Clinical Outcomes in Routine Evaluation – Outcome Measure (CORE-OM): measure assessing psychological distress and functioning.
- Mentalization Questionnaire (MZQ): measure assessing the ability to represent internal mental states.
- Personality Inventory for DSM-5 – Brief Form (PID-5-BF): measure assessing personality trait domains. All collected data will be entered into a dedicated study database using participant identification codes.

Statistical Analysis

Data analysis will be conducted using SPSS, SAS, and Mplus software.

Analyses will follow the intention-to-treat (ITT) principle, including all randomized participants according to their assigned group, regardless of adherence to the intervention.

Continuous variables will be described using mean and standard deviation or median and interquartile range (IQR), depending on data distribution. Categorical variables will be reported as frequencies and percentages.

Normality of distributions will be assessed through skewness, kurtosis, and the Kolmogorov-Smirnov test.

To compare groups after surgery while accounting for baseline differences, analysis of covariance (ANCOVA) models will be performed, with post-surgery outcomes as dependent variables and baseline scores as covariates.

The statistical model will include:

- Treatment group (experimental vs control).
- Baseline assessment value.
- Relevant clinical and demographic covariates, including age and CORE-OM Risk Scale score.

If assumptions of normality and homoscedasticity are not met, appropriate transformations or non-parametric alternatives will be considered.

Within-group changes over time will be evaluated using paired-samples t-tests when appropriate. Effect estimates will be reported with 90% confidence intervals. Statistical significance will be set at $p < 0.10$ (one-tailed).

Study Duration and Phases

Total study duration: 24 months.

- Months 1–18: participant recruitment and implementation of the study protocol, following approval by the Intercompany Territorial Ethics Committee of AOU Città della Salute e della Scienza of Torino.
- Months 3–24: data analysis and dissemination of results.

The recruitment period may be extended if the required sample size is not achieved.

Risk and Risk Management

The study procedures are not expected to pose risks to participants' physical health. However, participants may experience temporary psychological discomfort when discussing illness-related experiences, emotions, body image, or concerns related to surgery. Participants may also experience discomfort related to the application of biofeedback sensors. Participants will be informed that they may interrupt questionnaires, interviews, or biofeedback sessions at any time to discuss concerns with the clinician. The clinician's clinical training allows them to provide support, address distress, and answer participants' questions.

Confidentiality and Data Protection

Each participant will be assigned a unique alphanumeric identification code.

Participant identity and treatment allocation will only be accessible to research personnel involved in randomization and intervention delivery.

Outcome assessors and other study personnel will have access only to coded data. Data will be analyzed in pseudonymized form by the Department of Psychology of the University of Torino.

Study questionnaires will be stored securely for five years. The study database will be password-protected and accessible only to authorized researchers.

All data processing will comply with applicable regulations regarding personal data protection.