Statistical Analysis Plan

Title of the Study: Multimodal Prehabilitation Before Robotic-Assisted Radical Prostatectomy: A Randomized Controlled Trial on, Quality of Life, Functional Recovery and Psychological Well-being

Brief Title: Impact of a Multimodal Prehabilitation Program Before Robotic-assisted Radical Prostatectomy.

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Dataset: Ninety-five participants enrolled in a prospective, single centre, randomized controlled trial, including an intervention group undergoing multimodal prehabilitation and a control group receiving standard care. Outcomes assessments were conducted at five time points: baseline (prior to prehabilitation), after the prehabilitation period (pre-surgery), and at 1, 3, and 6 months postoperatively with outcomes measured with questionnaires or tests such as; EORTC QLQ-C30, EORTC QLQ-PR25, HADS, ICIQ IU SF, IIEF-5, 6MWT.

Proposed analyses:

1. Baseline Characteristics. Descriptive statistics to summarise baseline demographic and clinical characteristics including: Age at surgery (years), BMI (kg/m^2), ASA, PSA (ng/ml), cT stage, Biopsy higher ISUP, Prostate volume (cc), Operative time (min), Lymphadenectomy (Yes/No), neurovascular bundle (NVB) preservation (No NVB preservation, Unilateral, Bilateral).

Continuous variables will be summarized as medians with interquartile ranges (IQR). This include: Age at surgery (years), BMI (kg/m^2), PSA (ng/ml), Prostate volume (cc), Operative time (min).

Categorical variables will be reported as frequencies and percentages. This include: ASA (categories; I-II, III), cT stage (categories; cT1, cT2, cT3-4), biopsy higher ISUP (categories; 1, 2, 3, 4-5), Lymphadenectomy (Yes/No), NVB preservation (No NVB preservation, Unilateral, Bilateral).

Baseline characteristics will be presented stratified by study group. These data will be reported in Table 1. Baseline characteristics are summarized by study group without formal statistical testing for differences between groups (no hypothesis testing), in accordance with CONSORT recommendations for randomized trials.

2. Primary outcome.

- Does multimodal prehabilitation improve early postoperative health-related quality of life at 1 month following robotic-assisted radical prostatectomy compared with standard care?

Health-related quality of life (HRQoL) will be assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). For the primary outcome, the Global Health Status domain score of the EORTC QLQ-C30 will be analysed.

All EORTC QLQ-C30 and QLQ-PR25 domain and symptom scores will be calculated according to the official EORTC scoring manual. Raw scores will be linearly transformed to a 0–100 scale and will be treated as continuous variables. For functional and global health status scales, higher scores indicate better functioning or quality of life, whereas for symptom scales higher scores indicate greater symptom burden.

To assess whether multimodal prehabilitation improves early postoperative recovery, between-group differences in the Global Health Status score at 1 month after surgery will be analysed using analysis of covariance (ANCOVA). The EORTC QLQ-C30 global health status score at 1 month will be specified as the dependent variable, treatment group (prehabilitation vs standard care) as a fixed factor, and the corresponding baseline score as a continuous covariate. Global Health status score will be summarized and described using means (SD).

Treatment effects will be reported as adjusted mean differences with 95% confidence intervals and two-sided p-values.

The one-month outcome is defined as the assessment conducted at the participant's scheduled one-month follow-up visit. If a participant missed the scheduled appointment or requested a reschedule, a single additional opportunity was provided to complete the assessment within the following week. Participants who did not complete the assessment during this window were not included at the one-month time point, and follow-up proceeded to the next scheduled assessment (e.g., three months) using the same procedure. All repeated outcomes were assessed following the same procedure throughout the study.

Missing data

Missing outcome data will not be imputed, and analyses will be conducted using available cases in accordance with the intention-to-treat principle.

The extent of missing data will be described for each outcome and assessment time point, both overall and stratified by treatment group. Patterns of missingness will be explored stratified by treatment group, age (>65 vs ≤ 65) and baseline health-related quality of life with the global health status score.

3. Secondary Study Questions

-Does multimodal prehabilitation improve early postoperative recovery in additional HRQoL domains of the EORTC QLQ-C30 (physical, role, emotional, cognitive, and social functioning) at 1 month following surgery?

The different domains and scores will be summarized and described using means (SD). As the primary outcome, to assess whether multimodal prehabilitation improves early postoperative recovery, between-group differences in the other health-related quality of life domains of the EORTC QLQ-C30 (Physical/Role/Emotional/Cognitive/Social functioning) at 1 month after surgery will be analysed using analysis of covariance (ANCOVA). The EORTC QLQ-C30 domain at 1 month will be specified as the dependent variable, treatment group (prehabilitation vs standard care) as a fixed factor, and the corresponding baseline score as a continuous covariate. Treatment effects will be reported as adjusted mean differences with 95% confidence intervals and two-sided p-values.

-Does multimodal prehabilitation influence the trajectory of recovery in HRQoL domains over time compared with standard care?

In addition, longitudinal changes in EORTC QLQ-C30 HRQoL domain scores over time (baseline, preoperative, and 1, 3, and 6 months postoperatively) will be analysed using linear mixed-effects models to account for repeated measurements within participants. Domain scores will be specified as continuous dependent variables, with treatment group, time, and the group × time interaction included as fixed effects. Baseline scores will be included as covariates. The group × time interaction will be used to assess whether changes in HRQoL over time differ between the intervention and control groups. Adjusted mean differences with 95% confidence intervals and two-sided p-values will be reported.

- Is multimodal prehabilitation associated with improved early functional recovery (urinary continence, erectile function, physical performance, and psychological well-being) compared with standard care?

These outcomes are measured within the study with the following:

- Urinary continence (ICIQ-UI SF)

  International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form (ICIQ-UI SF).

  Urinary continence will be assessed using the International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form (ICIQ-UI SF). This questionnaire includes three scored items (assessing frequency, amount of leakage, and overall impact) and one non-scored self-diagnostic item. In this study, we will use only the three scored items, yielding a total score ranging from 0 to 21, which will be analyzed as a continuous variable. We will not perform categorical analyses (e.g., classifying 0 points as "continent" and >0 as "incontinent") as done in some published studies.

- Erectile function (IIEF-5)

  Erectile function will be evaluated using the International Index of Erectile Function – 5 items (IIEF-5). This questionnaire includes five items, each scored 1–5, resulting in a total score ranging from 5 to 25, with higher scores indicating better erectile function. For analysis, the total score will be categorized as ≥17 (normal or mild dysfunction) and <17 (moderate to severe dysfunction)**.**

- Physical performance (6-minute walk test)

  Physical performance will be assessed with the 6-minute walk test (6MWT)**,** measuring the total distance walked in meters over six minutes. The total distance walked will be treated as a continuous variable**.**

- Psychological well-being (Hospital Anxiety and Depression Scale)

Psychological well-being will be measured using the Hospital Anxiety and Depression Scale (HADS), which includes 14 items: seven assessing anxiety and seven assessing depression. Each item is scored 0–3, producing subscale scores ranging from 0 to 21. In this study, the anxiety and depression subscales will be analyzed independently, and the total HADS score will not be used. Both subscale scores will be analyzed as continuous variables.

- Disease-specific HRQoL (EORTC QLQ-PR25)

  Disease-specific health-related quality of life will be assessed using the EORTC QLQ-PR25 prostate cancer module. The questionnaire includes multiple subscales, including urinary symptoms, bowel symptoms, sexual activity and functioning, and hormone therapy-related symptoms. Items are scored 1–4 and linearly transformed to a 0–100 scale**,** with higher scores indicating either worse symptoms (for symptom scales) or better function (for function scales). Each subscale will be analyzed as a continuous variable**.**

The different scores will be summarized using means (SD), except for HADS and ICIQ-UI SF, which are often skewed toward 0; for these, medians (IQR) will be reported.

Analysis at 1 month: Between-group differe nces in functional recovery outcomes at 1 month postoperatively will be analyzed using analysis of covariance (ANCOVA)**.** Each outcome at 1 month will be specified as the dependent variable, treatment group (prehabilitation vs standard care) as a fixed factor, and the corresponding baseline score as a continuous covariate**.** Adjusted mean differences with 95% confidence intervals and two-sided p-values will be reported. Erectile function (IIEF-5) will be dichotomized (≥17 vs <17) and analyzed at 3 months postoperatively using binary regression models adjusted for baseline status.

Longitudinal analyses. To assess recovery trajectories over time, changes in these functional outcomes at baseline, preoperative, and 1, 3, and 6 months postoperatively will be analyzed using linear mixed-effects models to account for repeated measurements within participants as specified previously in this report

4. Exploratory and Perioperative Outcomes

Does prehabilitation enhance perioperative outcomes compared with the standard of care?

Exploratory outcomes include:

- In-hospital complications: Categorical variable (Yes/No).
- In-hospital complications grade: Assessed using the Clavien–Dindo classification, treated as a categorical variable (grades 0-1, 2, ≥3).
- In-hospital mortality: Categorical variable (Yes/No).
- Complications within 30 days after discharge: Assessed using the Clavien–Dindo classification, treated as a categorical variable (grades 0-1, 2, ≥3).
- Length of hospital stay: Continuous variable (days).
- Emergency department visit within 30 days: Categorical variable (Yes/No).
- Hospital readmission within 30 days: Categorical variable (Yes/No).

These outcomes will be summarized descriptively by study group. Continuous variables, such as length of hospital stay, will be reported as median and interquartile range (IQR), while categorical variables will be reported as counts and percentages (n, %). Between-group comparisons will be performed as follows: Categorical outcomes (in-hospital complications [Yes/No], in-hospital complication grade, in-hospital mortality, complications within 30 days after discharge, emergency department visits, and hospital readmission) will be compared using the Chi-square test. Length of hospital stay will be compared using the Mann–Whitney U test.

All analyses will follow the intention-to-treat (ITT) principle, including all randomized patients in the groups to which they were originally assigned, regardless of adherence to the intervention protocol. A two-sided p-value < 0.05 would be considered statistically significant.