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Multimodal Prehabilitation for Radical Cystectomy: Optimizing Physiological Resilience and Postoperative Recovery

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Abstract | **Original Research Article**

Background: Radical cystectomy (RC) is the standard treatment for muscle-invasive bladder cancer but is associated with high perioperative morbidity, affecting 50–65% of patients. This patient population is frequently characterized by advanced age, frailty, and malnutrition, which are further exacerbated by neoadjuvant chemotherapy (NAC). Prehabilitation has emerged as a multidisciplinary strategy to enhance physiological and psychological resilience before surgery. ***Objectives:*** This mini-review synthesizes current evidence regarding the components, clinical efficacy, and implementation challenges of prehabilitation programs in the RC population. ***Methods:*** We reviewed recent clinical trials, meta-analyses, and systematic reviews focusing on multimodal interventions—incorporating exercise, nutritional optimization, and psychological support—delivered during the preoperative window. ***Results:*** Multimodal programs consistently demonstrate improvements in functional capacity and health-related quality of life. Exercise interventions significantly enhance cardiorespiratory fitness and muscular strength, while preoperative immunonutrition has been shown to reduce surgical site infections and accelerate gastrointestinal recovery. Despite these functional gains, the impact on "hard" surgical outcomes remains inconclusive; while broader surgical oncology data suggest a reduction in overall complications, specific urologic meta-analyses have yet to definitively prove a reduction in length of stay or mortality. ***Implementation & Future Directions:*** While prehabilitation is safe and feasible with high adherence rates (80–100%), institutional barriers such as funding and time constraints remain. Current research, including the ENHANCE and INCyst trials, is focused on standardizing protocols and evaluating the role of digital health and home-based interventions. ***Conclusions:*** Prehabilitation is a promising strategy to optimize RC candidates. Although evidence for improved traditional surgical outcomes is still maturing, the benefits for physical recovery and quality of life support its integration into the standard care pathway for bladder cancer.

Keywords: Bladder Cancer, Radical Cystectomy, Prehabilitation, Exercise, Immunonutrition, Quality of Life.

INTRODUCTION

Radical cystectomy (RC) remains the standard surgical treatment for muscle-invasive bladder cancer (MIBC) and high-risk non-muscle-invasive disease that does not respond to intravesical therapy [1]. Despite advances in surgical techniques, such as robotic-assisted approaches and enhanced recovery after surgery (ERAS) protocols, RC is associated with significant perioperative morbidity, with 50- 65% of patients experiencing complications [2]. Patients undergoing RC are often older and have a high burden of comorbidities. They may also present with frailty, sarcopenia, and malnutrition. All of these factors are independently associated with adverse postoperative outcomes [3-4]. The preoperative period, which is often extended by neoadjuvant chemotherapy (NAC), provides an opportunity to optimize patient fitness. Prehabilitation, a multidisciplinary intervention designed to enhance physiological, nutritional, and psychological resilience before surgery, has emerged as a promising strategy to mitigate treatment-related functional decline and improve recovery [5-6].

METHODS

Data for this mini-review were identified by searches of MEDLINE, PubMed, and Google Scholar using the search terms "prehabilitation", "radical cystectomy", "bladder cancer", and "multimodal optimization". We prioritized randomized controlled trials, systematic reviews, and meta-analyses published between 2017 and 2026 to ensure the inclusion of the most contemporary evidence. Ongoing clinical trials

were identified through ClinicalTrials.gov. Only articles published in English were included, with a specific focus on multimodal interventions combining exercise, nutrition, and psychological support.

Current Evidence and Clinical Perspectives

Rationale for Prehabilitation in the Cystectomy Population

The rationale for prehabilitation before RC is based on the understanding that modifiable preoperative risk factors, such as poor cardiorespiratory fitness, malnutrition, smoking, and psychological distress, are strongly linked to perioperative complications, prolonged hospital stays, and impaired functional recovery [2,5]. Bladder cancer patients are particularly vulnerable. The median age at diagnosis is in the seventh decade, and the prevalence of severe malnutrition in RC cohorts ranges from 16% to 22% [4]. Furthermore, NAC, while conferring a survival benefit, may exacerbate preoperative deconditioning and frailty [7]. This window of opportunity during NAC is critical, rather than viewing chemotherapy as a period of inevitable decline, it can serve as a protected timeframe for active prehabilitation. Emerging pragmatic models, such as home-based programs delivered via digital health platforms, are currently being evaluated to maintain or even improve physical capacity during systemic treatment. Prehabilitation aims to build physiological reserve so that patients can better withstand the stress of major surgery and recover more rapidly.

Components of Prehabilitation Programs

Modern prehabilitation programs are increasingly multimodal, integrating exercise training, nutritional optimization, and psychological support [5-6]. A large network meta-analysis of 186 randomized controlled trials (RCTs) involving 15,684 surgical patients revealed that the exercise and nutrition components were the elements most likely to improve critical outcomes. The analysis also found that a combination of exercise, nutrition, and psychosocial prehabilitation yielded the greatest improvements in quality of life and physical recovery [8].

Exercise is the most extensively studied component of prehabilitation. Programs typically incorporate both aerobic and resistance training at moderate to vigorous intensity, prescribed two to three times per week for three to six weeks [9-10]. A systematic review of prehabilitation exercises before urologic cancer surgery revealed that all of the included studies demonstrated significant improvements in cardiorespiratory fitness. Additionally, four out of five studies that evaluated quality of life observed significant improvements [11]. A prospective study of 20 patients undergoing open RC found that a supervised, multimodal exercise program lasting a median of 3.5 weeks produced significant improvements in leg press strength (16%), 6-minute walk test distance (8%), timed up-and-go performance (12%), and chair rise performance (10%) with no exercise-related adverse events [9].

A phase I/II trial of 54 sedentary patients aged 60 years and older demonstrated that a 4-week supervised exercise program was feasible (80.4% completion rate) and safe, resulting in sustained improvements in general and mental health at 90 days postsurgery [12].

Malnutrition is prevalent in the RC population and is associated with increased inflammatory markers, skeletal muscle breakdown, and immune dysfunction [4]. Preoperative immunonutrition, which typically involves formulas enriched with arginine, omega-3 fatty acids, and nucleotides, has shown promise in reducing postoperative infectious complications. A retrospective study of 204 RC patients found that preoperative L-arginine-based immunonutrition was an independent predictor of reduced postoperative infection (OR 0.35, $p = 0.02$) [13]. A pilot randomized controlled trial (RCT) of 29 men demonstrated that specialized immunonutrition shifted the Th1-Th2 immune balance, lowered peak interleukin-6 levels, and prevented arginine depletion compared to standard oral supplements [14]. A retrospective cohort study of 86 patients showed that preoperative immunonutrition significantly reduced surgical site infections after RC and ileal conduit (OR 0.14, $p = 0.019$) [15]. A recent RCT of 74 patients found that structured perioperative nutritional optimization significantly accelerated gastrointestinal recovery (time to flatus: 39.6 vs. 64.8 hours, $p = 0.001$), reduced length of stay (7.78 vs. 10.59 days, $p = 0.002$), and preserved skeletal muscle mass [16].

Anxiety and depression are common among patients awaiting RC and are associated with poorer surgical outcomes [2]. Although the evidence base specific to RC remains limited, psychological interventions, including stress management training, cognitive behavioral strategies, and patient education, are increasingly incorporated into multimodal programs. A scoping review of RCTs in bladder cancer found that eight of eleven trials involving psychological support yielded statistically significant improvements in outcomes of interest [17].

Evidence for Clinical Outcomes

The impact of prehabilitation on "hard" surgical outcomes in the RC population remains an area of active investigation, with results that are promising but not yet definitive.

The most consistent benefit of prehabilitation before RC surgery is an improvement in quality of life and physical function. A 2025 systematic review and meta-analysis of ten studies ($n = 564$) found that preoperative exercise significantly improved postoperative quality-of-life scores (SMD = 0.62; 95%

CI: 0.44–0.80; p < 0.001), with the greatest improvements seen with combined preoperative and postoperative exercise [18]. A randomized trial with a one-year follow-up of 107 patients demonstrated that prehabilitation significantly improved physical function (muscle leg power, p = 0.04), lean body mass (p = 0.047), and body cell mass (p = 0.03) one year after surgery [19].

A meta-analysis of 27 RCTs involving 2,532 surgical oncology patients undergoing major abdominal surgery revealed that prehabilitation was associated with significantly lower odds of postoperative complications (OR: 0.60; 95% CI: 0.46–0.78; p = 0.01), though no significant differences were observed in length of stay or readmission rates [20]. However, an updated meta-analysis focused specifically on unimodal exercise prehabilitation found that preoperative exercise was not effective in reducing complications or length of stay for genitourinary cancer patients. This finding contrasts with the significant benefits observed in lung cancer surgery [21]. A narrative review of RCTs in urologic surgery concluded that single-modality interventions had no effect on traditional surgical outcomes, such as complications and length of stay. However, multimodal approaches were effective and safe for preserving functional capacity [5]. Implementing a comprehensive prehabilitation program at a high-volume center with 82 patients showed a modest decline in resource utilization and length of stay after implementation, with 30-day and 30- to 90-day complication rates of 56% and 40%, respectively [22].

However, a systematic review in European Urology noted that, to date, no trials have demonstrated a reduction in postsurgical complications, mortality, length of stay, or readmission rates following prehabilitation exercise interventions, particularly for urologic cancer surgery [11]. A small comparative study of 16 prehabilitation patients versus 175 controls found no significant differences in length of stay, readmission rates, or complications, though the study was severely limited by low referral rates [23]. Overall, the certainty of evidence across prehabilitation research remains low to very low due to risk of bias at the trial level, small sample sizes, and imprecision [8].

Feasibility and Implementation

Multiple studies have demonstrated that prehabilitation before RC is feasible, safe, and well-tolerated. Adherence rates in supervised programs range from 80% to 100%, with no exercise-related adverse events reported across studies [9,12,22]. A comprehensive prehabilitation program implemented as standard of care at a high-volume referral center achieved 100% malnutrition screening, 82% nutritional supplement consumption, and 52% preoperative physical therapy attendance [22].

Key barriers to widespread adoption include lack of institutional funding and resources (reported by 39.4% of hospitals in an international survey), low institutional interest, cost, time constraints imposed by the interval between diagnosis and surgery, intensity of in-person interventions, and overly restrictive inclusion criteria [3,24]. Socioeconomic disparities and health literacy also influence engagement, with patients from disadvantaged backgrounds less likely to participate despite having worse perioperative outcomes [25].

To mitigate these disparities, the integration of digital health technologies and tele-prehabilitation offers a scalable solution to reach underserved populations. By reducing the need for frequent hospital visits and providing structured, home-based guidance, these tools can improve engagement and help bridge the gap in perioperative outcomes between different socioeconomic groups.

Innovative solutions are being explored to overcome these barriers. The "Get Moving Trial" is evaluating a pragmatic, home-based prehabilitation program delivered via the ExerciseRx smartphone app, prescribing personalized 20-minute exercise sessions 4 times weekly during NAC, before RC, and for 90 days post-RC [3]. Qualitative research with bladder cancer survivors has identified that structured exercise plans, provider encouragement, objective fitness measurements, and digital health technologies are key motivators for patient engagement [26].

The clinical integration of prehabilitation into the RC pathway requires a nuanced, risk-stratified approach. While multimodal programs show clear functional benefits, the 'one-size-fits-all' model may face significant logistical hurdles, including institutional costs and the limited time-window during neoadjuvant chemotherapy. Future protocols should prioritize high-risk phenotypes, specifically patients presenting with baseline frailty, sarcopenia, or severe malnutrition, as these individuals likely stand to gain the most from intensive physiological optimization. Moreover, the transition from supervised, hospital-based sessions to pragmatic, home-based digital interventions, such as the ExerciseRx platform, represents a vital step toward ensuring equitable access and long-term adherence in the elderly bladder cancer population. Moving forward, the synergy between prehabilitation and modern systemic therapies, including immunotherapy and antibody-drug conjugates, will be a defining frontier in holistic perioperative care.

Ongoing and Future Research

Several large-scale RCTs are underway to provide more definitive evidence. The ENHANCE trial (NCT05480735) is a multicenter RCT in the Netherlands randomizing 154 patients to a 3–6 week multimodal prehabilitation program versus standard care, with the primary outcome of Clavien-Dindo grade ≥2 complications within 90 days [2]. The INCyst trial (NCT05726786) is a multicenter RCT of 232 patients

evaluating 7-day preoperative immunonutrition versus standard care, with translational endpoints including immune response and microbiota composition [27]. These trials are expected to provide higher-quality evidence to guide clinical practice.

Future research priorities include standardization of prehabilitation protocols and outcome measures, identification of patients most likely to benefit through risk stratification, cost-effectiveness analyses, and investigation of the interaction between prehabilitation and evolving perioperative systemic therapies such as perioperative immunotherapy and enfortumab vedotin-pembrolizumab combinations [1].

Furthermore, addressing the current heterogeneity in prehabilitation protocols remains a top priority. Establishing standardized "core outcome sets", which include both traditional surgical metrics and patient-reported functional measures, will be essential for conducting high-quality meta-analyses and developing evidence-based clinical guidelines.

Conclusion

Prehabilitation before radical cystectomy is a safe, feasible, and promising strategy to optimize patient fitness and improve quality of life in a population with high surgical morbidity. The strongest evidence supports multimodal programs combining exercise, nutritional optimization, and psychological support for improving functional capacity and quality of life. While the impact on traditional surgical outcomes such as complications and length of stay has not yet been conclusively demonstrated in the RC population, broader surgical oncology data and emerging bladder cancer-specific trials are encouraging. As the treatment landscape for MIBC evolves with the integration of neoadjuvant and perioperative systemic therapies, prehabilitation represents an important complementary approach to holistic patient optimization. Results from ongoing large-scale RCTs will be critical in defining the role of prehabilitation as a standard component of the RC care pathway.

Declaration

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